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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C07D 401/04, 413/04, 471/04, 471/10, A61K 31/415, 31/42, 31/445, 31/44, 31/47, 31/505

A1

(11) International Publication Number: **WO 95/28397**

(43) International Publication Date: 26 October 1995 (26.10.95)

(21) International Application Number: PCT/US95/04590

(22) International Filing Date: 13 April 1995 (13.04.95)

(30) Priority Data:
229,276 14 April 1994 (14.04.94) US

(60) Parent Application or Grant
(63) Related by Continuation
US 229,276 (CIP)
Filed on 14 April 1994 (14.04.94)

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(81) Designated States: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, IS, JP, KG, KR, KZ, LK, LR, LT, LV, MD, MG, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TT, UA, US, UZ, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ, UG).

Published
With international search report.

(54) Title: ALPHA1C ADRENERGIC RECEPTOR ANTAGONISTS

(57) Abstract

This invention relates to certain novel compounds and derivatives thereof, their synthesis, and their use as selective alpha1C adrenergic receptor antagonists. One application of these compounds is in the treatment of benign prostatic hypertrophy. These compounds are selective in their ability to relax smooth muscle tissue enriched in the alpha1C receptor subtype without at the same time inducing orthostatic hypotension. One such tissue is found surrounding the urethral lining. Therefore, one utility of the instant compounds is to provide acute relief to males suffering from benign prostatic hyperplasia, by permitting less hindered urine flow. Another utility of the instant compounds is provided by combination with a human 5-alpha reductase inhibitory compound, such that both acute and chronic relief from the effects of benign prostatic hyperplasia are achieved.

Serial No. 09/402,244

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VN	Viet Nam

TITLE OF THE INVENTION
ALPHA1C ADRENERGIC RECEPTOR ANTAGONISTS

BACKGROUND OF THE INVENTION

1. Field of the Invention:

This application is a continuation-in-part of U.S. Serial No. 08/229,276, filed April 14, 1995, the contents of which are hereby incorporated by reference.

This invention relates to certain novel compounds and derivatives thereof, their synthesis, and their use as selective alpha-1c adrenoceptor antagonists. One application of these compounds is in the treatment of benign prostatic hypertrophy. These compounds are selective in their ability to relax smooth muscle tissue enriched in the alpha1C receptor subtype without at the same time inducing orthostatic hypotension. One such tissue is found surrounding the urethral lining. Therefore, one utility of the instant compounds is to provide acute relief to males suffering from benign prostatic hyperplasia, by permitting less hindered urine flow. Another utility of the instant compounds is provided by combination with a human 5-alpha reductase inhibitory compound, such that both acute and chronic relief from the effects of benign prostatic hyperplasia are achieved. Other advantages of the instant compounds are appreciated from the complete disclosure.

ii. Background:

Human adrenergic receptors are integral membrane proteins which have been classified into two broad classes, the alpha and the beta adrenergic receptors. Both types mediate the action of the peripheral sympathetic nervous system upon binding of catecholamines, norepinephrine and epinephrine.

Norepinephrine is produced by adrenergic nerve endings, while epinephrine is produced by the adrenal medulla. The binding affinity of adrenergic receptors for these compounds forms one basis of the classification: alpha receptors bind norepinephrine more strongly

than epinephrine and much more strongly than the synthetic compound isoproterenol. The binding affinity of these hormones is reversed for the beta receptors. In many tissues, the functional responses, such as smooth muscle contraction, induced by alpha receptor activation are opposed to responses induced by beta receptor binding.

Subsequently, the functional distinction between alpha and beta receptors was further highlighted and refined by the pharmacological characterization of these receptors from various animal and tissue sources. As a result, alpha and beta adrenergic receptors were further subdivided into α_1, α_2, β_1, and β_2 subtypes. Functional differences between α_1 and α_2 receptors have been recognized, and compounds which exhibit selective binding between these two subtypes have been developed. Thus, in WO 92/0073, the selective ability of the R(+) enantiomer of terazosin to selectively bind to adrenergic receptors of the alpha 1 subtype was reported. The α_1/α_2 selectivity of this compound was disclosed as being significant because agonist stimulation of the α_2 receptors was said to inhibit secretion of epinephrine and norepinephrine, while antagonism of the α_2 receptor was said to increase secretion of these hormones. Thus, the use of non-selective alpha-adrenergic blockers, such as phenoxybenzamine and phentolamine, is limited by their α_2 adrenergic receptor mediated induction of increased plasma catecholamine concentration and the attendant physiological sequelae (increased heart rate and smooth muscle contraction).

For a general background on the α-adrenergic receptors, the reader's attention is directed to Robert R. Ruffolo, Jr., <u>α-Adrenoreceptors: Molecular Biology, Biochemistry and Pharmacology</u>, (<u>Progress in Basic and Clinical Pharmacology</u> series, Karger, 1991), wherein the basis of α_1/α_2 subclassification, the molecular biology, signal transduction (G-protein interaction and location of the significant site for this and ligand binding activity away from the 3'-terminus of alpha adrenergic receptors), agonist structure-activity relationships, receptor functions, and therapeutic applications for compounds exhibiting α-adrenergic receptor affinity was explored.

The cloning, sequencing and expression of alpha receptor subtypes from animal tissues has led to the subclassification of the α_1 receptors into α_1A, (Lomasney, et al., J. Biol. Chem., 266:6365-6369 (1991), rat α_1A; Bruno et al., BBRC, 179:1485-1490 (1991), human α_1A), α_1B (Cotecchia, et al., PNAS, 85;7159-7163 (1988), hamster α_1B; Libert, et al., Science, (1989), dog α_1B; Ramarao, et al., J. Biol. Chem., 267:21936-21945 (1992), human α_1B), and most recently, in a study using bovine brain, a new α_1C subtype was proposed (Schwinn, et al., J. Biol. Chem., 265:8183-8189, 1990; Hirasawa et al., BBRC 195:902-909 (1993), described the cloning, functional expression and tissue distribution of a human α_1C adrenergic receptor; Hoehe et al., Human Mol. Genetics 1(5):349 (8/92) noted the existence of a two-allele Pst1 restriction fragment polymorphism in the α_1C adrenergic receptor gene; another study suggests that there may even be an alpha-1D receptor subtype, see Perez et al., Mol. Pharm.., 40:876-883, 1992). Each α_1 receptor subtype exhibits its own pharmacologic and tissue specificities. Schwinn and coworkers noted that the cloned bovine α_1C receptor exhibited pharmacological properties proposed for the α_1A subtype. Nonetheless, based on its non-expression in tissues where the α_1A subtype is expressed, and its sensitivity to chloroethylclonidine, the receptor was given a new designation.

The differences in the α–adrenergic receptor subtypes have relevance in pathophysiologic conditions. Benign prostatic hypertrophy, BPH, is an illness typically affecting men over fifty years of age, increasing in severity with increasing age. The symptoms of the condition include, but are not limted to, increased difficulty in urination and sexual dysfunction. These symptoms are induced by enlargement, or hypertrophy, of the prostate gland. As the prostate increases in size, it impinges on free-flow of fluids through the male urethra. Concommitantly, the increased noradrenergic innervation of the enlarged prostate leads to an increased adrenergic tone of the bladder neck and urethra, further restricting the flow of urine through the urethra.

The mechanism of prostatic hypertrophy is well understood. The male hormone, 5α-dihydrotestosterone has been identified as the principal culprit. The continual production of 5α-dihydrotestosterone by the male testes induces incremental growth of the prostate gland throughout the life of the male. Beyond the age of about fifty years, in many men, this enlarged gland begins to obstruct the urethra with the pathologic symptoms noted above.

The elucidation of the mechanism summarized above has resulted in the recent development of effective agents to control, and in many cases reverse, the pernicious advance of BPH. In the forefront of these agents is Merck & Co., Inc.s' product PROSCAR® (finasteride). The effect of this compound is to inhibit the enzyme testosterone 5-alpha reductase, which converts testosterone into 5α-dihydrotesterone, resulting in a reduced rate of prostatic enlargement, and often reduction in prostatic mass.

The development of such agents as PROSCAR® bodes well for the long-term control of BPH. However, as may be appreciated from the lengthy development of the syndrome, its reversal also is not immediate. In the interim, those males suffering with BPH continue to suffer, and may in fact lose hope that the agents are working sufficiently rapidly.

In response to this problem, one solution is to identify pharmaceutically active compounds which complement slower-acting therapeutics by providing acute relief. Agents which induce relaxation of the urethral smooth muscle, by binding to alpha-1 adrenergic receptors, thus reducing the increased adrenergic tone due to the disease, would be good candidates for this activity. Thus, one such agent is alfuzosin, which is reported in EP 0 204597 to induce urination in cases of prostatic hypertrophy. Likewise, in WO 92/0073, the selective ability of the R(+) enantiomer of terazosin to bind to adrenergic receptors of the α_1 subtype was reported. In addition, in WO 92/161213, hereby incorporated by reference, combinations of 5-alpha-reductase inhibitory compounds and alpha1-adrenergic receptor blockers (terazosin, doxazosin, prazosin, bunazosin, indoramin,

alfuzosin) were disclosed. However, no information as to the $\alpha 1A$, $\alpha 1B$, or $\alpha 1C$ subtype specificity of these compounds was provided as these refinements were not yet available. Current therapy for BPH uses existing non-selective alpha-1 antagonists such as prazosin (Minipress, Pfizer) or Terazosin (Hytrin, Abbott). These non-selective antagonists suffer from side effects related to antagonism of the alpha-1a and alpha-1b receptors in the peripheral vasculature, eg., orthostatic hypotension and syncope.

Typically, identification of active compounds is through use of animal tissues known to be enriched in adrenergic receptors. Thus, rat tissues have been used to screen for potential adrenergic receptor antagonists. However, because of species variability, compounds which appear active in animal tissue may not be active or sufficiently selective in humans. This results in substantial wastage of time and effort, particularly where high volume compound screening programs are employed. There is also the danger that compounds, which might be highly effective in humans, would be missed because of their absence of appreciable affinity for the heterologous animal receptors. In this regard, it has been noted that even single amino acid changes between the sequence of biologically active proteins in one species may give rise to substantial pharmacological differences. Thus, Fong et al., (J. Biol. Chem., 267:25668-25671, 1992) showed that there are 22 divergent amino acid residues between the sequence of the human neurokinin-1 receptor and the homologous rat receptor. They further showed, in studies with mutant receptors, that substitution of only two amino acid residues was both necessary and sufficient to reproduce the rat receptor's antagonist binding affinity in the human receptor. Oksenberg et al., (Nature, 360:161-163, 1992) showed that a single amino-acid difference confers major pharmacological variation between the human and the rodent 5-hydroxytryptamine receptors. Likewise, Kuhse et al., (Neuron, 5:867-873, 1990) showed that a single amino-acid exchange alters the pharmacology of the neonatal rat glycine receptor subunit. This difficulty and unpredictability has resulted in a need for a

compound screen which will identify compounds that will be active in humans.

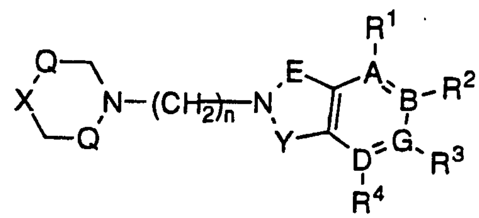
These problems are solved by cloning the human adrenergic receptor of the $\alpha 1C$ subtype and the use of a screening assay which enables identification of compounds which specifically interact with the human $\alpha 1C$ adrenergic receptor. Marshall et al (Br. J. Pharm., 107:327 (1992)) speculated that compounds which specifically interact with the $\alpha 1C$ adrenergic receptor may be responsible for contraction of the human prostate. As disclosed in the instant patent disclosure, a cloned human $\alpha 1C$ adrenergic receptor and a method for identifying compounds which bind the human $\alpha 1C$ receptor has now made possible the identification of specific human $\alpha 1C$ adrenergic receptor antagonists. In the instant patent disclosure, we reveal novel compounds which we have discovered specifically bind the human $\alpha 1C$ receptor. These compounds are further tested for binding to other human alpha 1 receptor subtypes, as well as counterscreened against other types of receptors, thus defining the specificity of the compounds for the human $\alpha 1C$ adrenergic receptor.

Compounds of his invention are used to reduce the acute symptoms of BPH. Thus, compounds of this invention may be used alone or in conjunction with a more long-term anti-BPH therapeutics, such as testosterone 5-alpha reductase inhibitors, including PROSCAR® (finasteride). Aside from their utility as anti-BPH agents, these compounds may be used to induce highly tissue-specific, localized $\alpha 1C$ adrenergic receptor blockade whenever this is desired. Effects of this blockade include reduction of intra-ocular pressure, control of cardiac arrhythmias, and possibly a host of alpha-1C receptor mediated central nervous system events.

SUMMARY OF THE INVENTION

This invention provides compounds for the treatment of urinary obstruction caused by benign prostatic hypertropy (also known as benign prostatic hyperplasia or BPH). The compounds selectively antagonize the human alpha-1C adrenergic receptor at nanomolar and

subnanomolar concetrations while exhibiting at least ten fold lower affinity for the alpha1A and alpha1B human adrenergic receptor and many other G-protein coupled receptors. This invention has the advantage over non-selective alpha-1 adrenoceptor antagonists of reduced side effects related to peripheral adrenergic blockade. Such side effects include orthostatic hypotension, syncope, lethargy etc. These compounds have the structure:



and a pharmaceutically acceptable salt, prodrug, polymorph, or metabolite thereof wherein:

n is an integer from 3 to 5;

Y represents carbonyl, sulphonyl, $-CO-CH_2-$, or $-CO-NR^{12}-$;

R^{12} is hydrogen, substituted or unsubstituted lower alkyl, substituted or unsubstituted phenyl;

E is carbonyl or sulphonyl;

A, B, G, D are independently carbon or nitrogen;

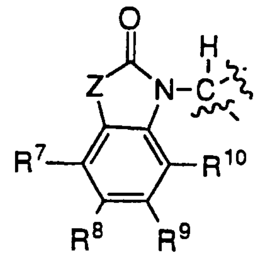
R^1-R^4 are independently selected from the group consisting of hydrogen; halogen; nitro; amino; substituted or unsubstituted lower alkyl; perhalogenated lower alkyl; substituted or unsubstituted lower alkoxy; sulfonyl alkyl; and substituted or unsubstituted aryl or heteroaryl; with the proviso that if any of A, B, G, or D is a nitrogen, then the substituent R group is not present;

Q is, independently, $(-CH_2-)_r$, -NH-, S, or O;

r is 0-3; and

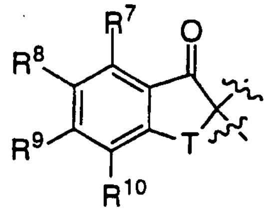
X is

a)



, or

b)

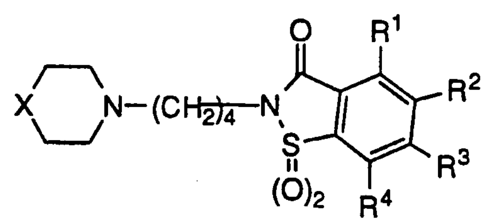


T is nitrogen, carbon, lower alkylene of one to three carbons or lower alkenylene of one to three carbons;

R^7-R^{10} are independently selected from the group consisting of hydrogen, lower alkyl, lower alkenyl, and lower alkoxy; and

Z is O, S, CH_2, CH_2O, OCH_2, SCH_2, lower alkylene, lower alkenylene, NH, or NMe.

In one embodiment of the invention, the compound has the structure:



and a pharmaceutically acceptable salt, prodrug, polymorph or metabolite thereof, wherein all substituents are as defined above.

These compounds may be used to advantage whenever specific blockade of the alpha1C adrenergic receptor is desirable, and are particularly useful in the treatment of benign prostatic hyperplasia (BPH) and for inhibiting contraction of prostate tissue, either alone or in combination with other active compounds. One preferred combination therapy includes the use of compounds described herein in conjuction with a compound effective to inhibit testosterone 5-alpha reductase.

BRIEF DESCRIPTION OF THE FIGURES

Fig. 1: Sequence of cDNA obtained by PCR of human heart mRNA, SEQ. ID:4:.

Fig. 2: Comparison of the open reading frame obtained from human heart, SEQ ID:5:, and the bovine alpha-1C adrenergic receptor sequence, SEQ. ID:6:.

Fig. 3: Sequence of cDNA obtained by screening a human hippocampus cDNA library using the heart mRNA derived sequence from figure 1, SEQ. ID:7:

Fig. 4: Sequence of 3' coding region of human alpha-1C gene, obtained by PCR amplification of a human genomic DNA library with oligonucleotides, SEQ. ID:10:.

Fig. 5: Sequence of the ligated portions of human alpha-1C DNA shown in figures 3 and 4, SEQ. ID:11:.

Fig. 6: The amino acid sequence of the human alpha-1C adrenergic receptor, SEQ ID:12:.

Fig. 7: The alignment of the nucleotide and amino acid sequence of the human alpha-1C adrenergic receptor, showing the 5'-untranslated region, SEQ. ID:11: and SEQ. ID:12:.

Fig. 8: Expression of the human alpha-1C adrenergic receptor in COS cells: Binding data using membranes from cells transfected with the expression vector alone and the expression vector containing the human alpha-1C adrenergic receptor coding sequences.

Fig. 9: Binding curves of compounds using membranes from COS cells transfected with the human alpha-1C adrenergic receptor containing expression vector.

Fig. 10: Nucleotide sequence of the human alpha1A receptor, SEQ. ID:13:

Fig. 11: Amino acid sequence of the human alpha1A adrenergic receptor, SEQ. ID:14:

Fig. 12: Partial sequence of the human alpha1B adrenergic receptor, SEQ. ID:17:

Fig. 13: Partial sequence of the human alpha1B adrenergic receptor, SEQ. ID:20:

Fig. 14: Partial sequence of the human alpha1B adrenergic receptor, SEQ. ID:23:

Fig. 15: Composite human/rat alpha1B adrenoreceptror, SEQ. ID:24:

Fig. 16: Amino acid sequence of the composite human/rat alpha1B adrenergic receptor, SEQ. ID:25:

Fig. 17: Binding curves of compounds using membranes from COS cells transfected with the human alpha1A, 1B, and 1C adrenergic receptor expression vectors.

Fig. 18: Sequence of truncated human alpha1C adrenergic receptor, SEQ. ID:26:.

Fig. 19: Nucleotide sequence of the human $\alpha 1C$ adrenergic receptor having a Pst1 site, SEQ.ID:27:.

Fig. 20: Amino acid sequence of the human $\alpha 1C$ adrenergic receptor encoded by the Pst1 site encoding allele, SEQ.ID:28:.

Fig. 21: Alignment of the nucleotide and amino acid sequences of figures 19 and 20, SEQ.ID:27: and SEQ.ID:28:.

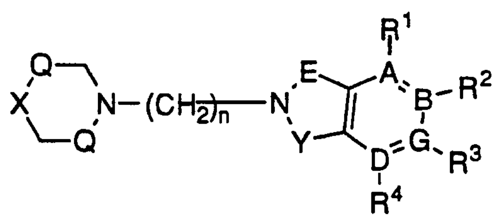
FIG. 22: Nucleotide sequence of the human $\alpha 1A$ adrenergic receptor, Seq.ID:29:.

Fig. 23: Amino acid sequence of the human $\alpha 1A$ adrenergic receptor, SEQ.ID:30:.

Fig. 24: Alignment of the nucleotide and amino acid sequences of figures 22 and 23, SEQ.ID:29: and SEQ.ID:30:.

DETAILED DESCRIPTION OF THE INVENTION

Compounds of this invention have the structure:



and a pharmaceutically acceptable salt, prodrug, polymorph, or metabolite thereof wherein:

n is an integer from 3 to 5;

Y represents carbonyl, sulphonyl, $-CO-CH_2-$, or $-CO-NR^{12}-$;

R^{12} is hydrogen, substituted or unsubstituted lower alkyl, substituted or unsubstituted phenyl;

E is carbonyl or sulphonyl;

A, B, G, D are independently carbon or nitrogen;

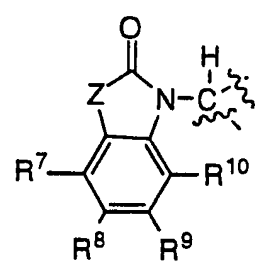
R^1-R^4 are independently selected from the group consisting of hydrogen; halogen; nitro; amino; substituted or unsubstituted lower alkyl; perhalogenated lower alkyl; substituted or unsubstituted lower alkoxy; sulfonyl alkyl; and substituted or unsubstituted aryl or heteroaryl; with the proviso that if any of A, B, G, or D is a nitrogen, then the substituent R group is not present;

Q is, independently, $(-CH_2-)_r$, -NH-, S, or O;

r is 0-3; and

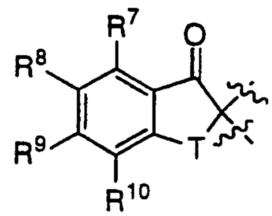
X is

a)



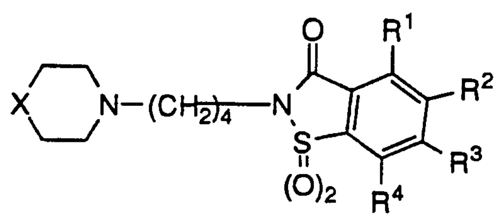
, or

b)



T is nitrogen, carbon, lower alkylene of one to three carbons or lower alkenylene of one to three carbons;
R^7-R^{10} are independently selected from the group consisting of hydrogen, lower alkyl, lower alkenyl, and lower alkoxy; and
Z is O, S, CH_2, CH_2O, OCH_2, SCH_2, lower alkylene, lower alkenylene, NH, or NMe.

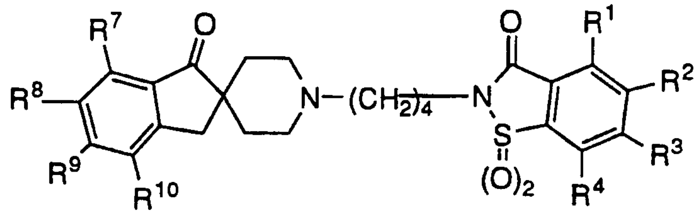
In one embodiment of the invention, the compound has the structure:



and a pharmaceutically acceptable salt, prodrug, polymorph or metabolite thereof, wherein all substituents are as defined above.

As used herein, the term lower alkyl, lower alkylene, or lower alkoxy means a substituted or unsubstituted, straight or branched chain of one to eight carbons. As used herein, a substituted group means that the group is halogenated, perhalogenated, particularly $-CF_3$, alkylated, alkoxylated, or is substituted with an aryl or heteroaryl. The term sulfonyl alkyl means a sulfonyl lower alkyl.

In a class of this embodiment of this invention, the compound is a piperidyl benzoxazinone substituted butyl saccharine or a spiroindanyl piperidine substituted butyl saccharine. In this embodiment of the invention, the compound is selected from:



and

wherein all variables are as previously defined. In specific embodiments of this invention, one of R^1-R^4 is preferably an electron withdrawing group such as the nitro group, a halogen or a halogenated alkyl which substituents we have discovered contribute to improved bioavailability.

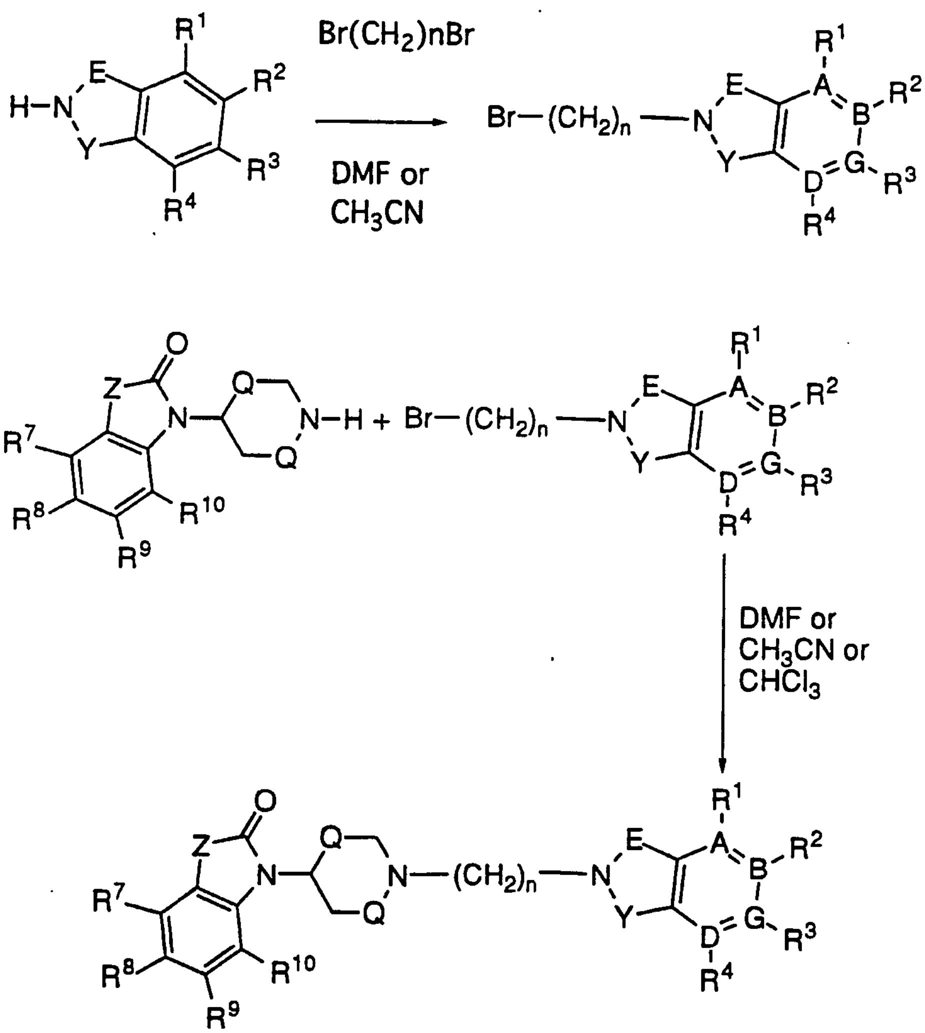
Representative compounds of this invention exhibit high selectivity for the human alpha1C adrenergic receptor and are therefore useful for treating benign prostatic hyperplasia and for inhibiting contraction of prostate tissue. One implication of this selectivity for the human alpha1C adrenergic receptor is that these compounds display selectivity for lowering intraurethral pressure without substantially affecting diastolic blood pressure.

Representative compounds of this invention display submicromolar affinity for the human alpha1C adrenergic receptor subtype while displaying at least ten-fold lower affinity for the human alpha1A and alpha1B adrenergic receptor subtypes, and many other G-protein coupled human receptors. Particular representative compounds of this invention exhibit nanomolar and subnanomolar affinity for the human alpha1C adrenergic receptor subtype while displaying at least 30 fold lower affinity for the human alpha1A and alpha1B adrenergic receptor subtypes, and many other G-protein coupled human receptors. Representative compounds of this invention exhibit Ki's for human alpha1C adrenergic receptors over a 500 fold lower than for the human alpha1A or alpha1B adrenergic receptors, while exhibiting greater than 300 fold selectivity for the human alpha1C adrenergic receptor over all other human G-protein coupled receptors tested (including serotonin,

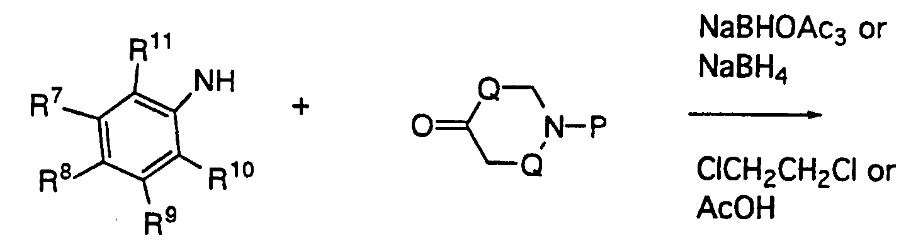
dopamine, alpha 2 adrenergic, beta adrenergic or muscarinic receptors). Furthermore, representative compounds of this invention exhibit good bioavailability in known animal models (approximately 30% in dogs and 16% in rats). These indicia are expected to provide good indications of bioavailability in humans.

Compounds of this invention are prepared by a two step alkylation process beginning with a saccharine or substituted saccharine (referred to as "the saccharine moiety") prepared according to methods known in the art (see for example US Patents 4,818,756; 4,937,343; 4,988,809 and 5,187,276, hereby incorporated by reference for this purpose). Preparation of spiropiperidines used herein in the preparation of compounds of this invention is described, for example, in published European Patent Application 90313262.9 (publication number 0 431 943 A2, 6/12/91, herein incorporated by reference for this purpose). The saccharine moiety is alkylated with a reagent such as 1,4-dibromobutane, or a similar reagent, to form the butyl-saccharine moiety (see Scheme 1 below). The butyl saccharine is then alkylated with a piperidinyl benzoxazinone (prepared as shown in Scheme 2 below) or with a spiroindanyl piperidine (prepared as shown in Scheme 3 below) to form the active compounds of this invention (see Scheme 1 below). These steps are further defined with reference to the following schemes, and the synthetic examples appended hereto. It should be understood that the specific solvents, catalysts and reactants could be substituted by analogous reagents by those skilled in the art. All substituents are as defined above:

Scheme 1

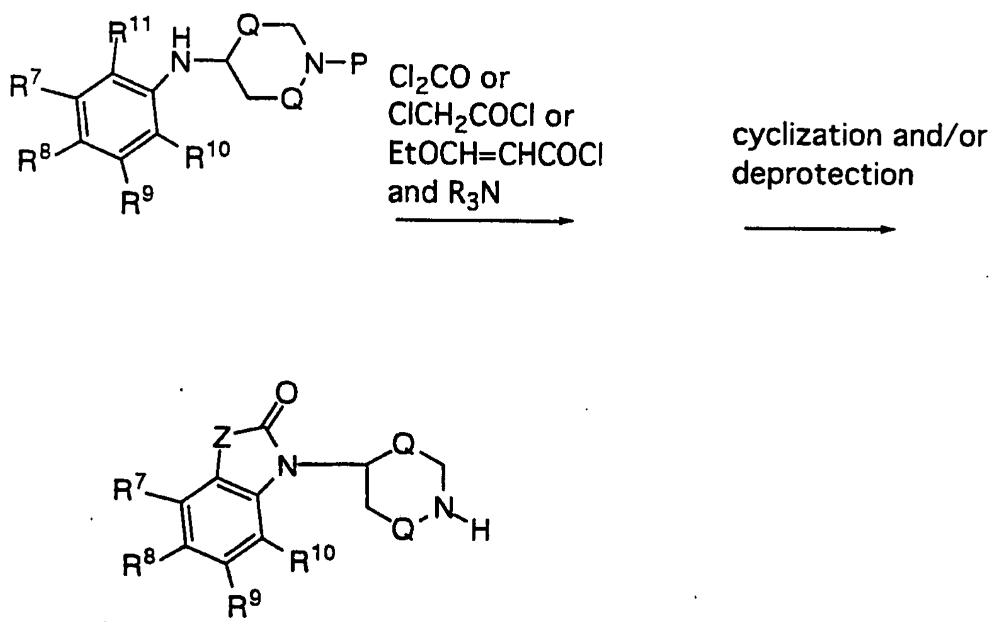


Scheme 2

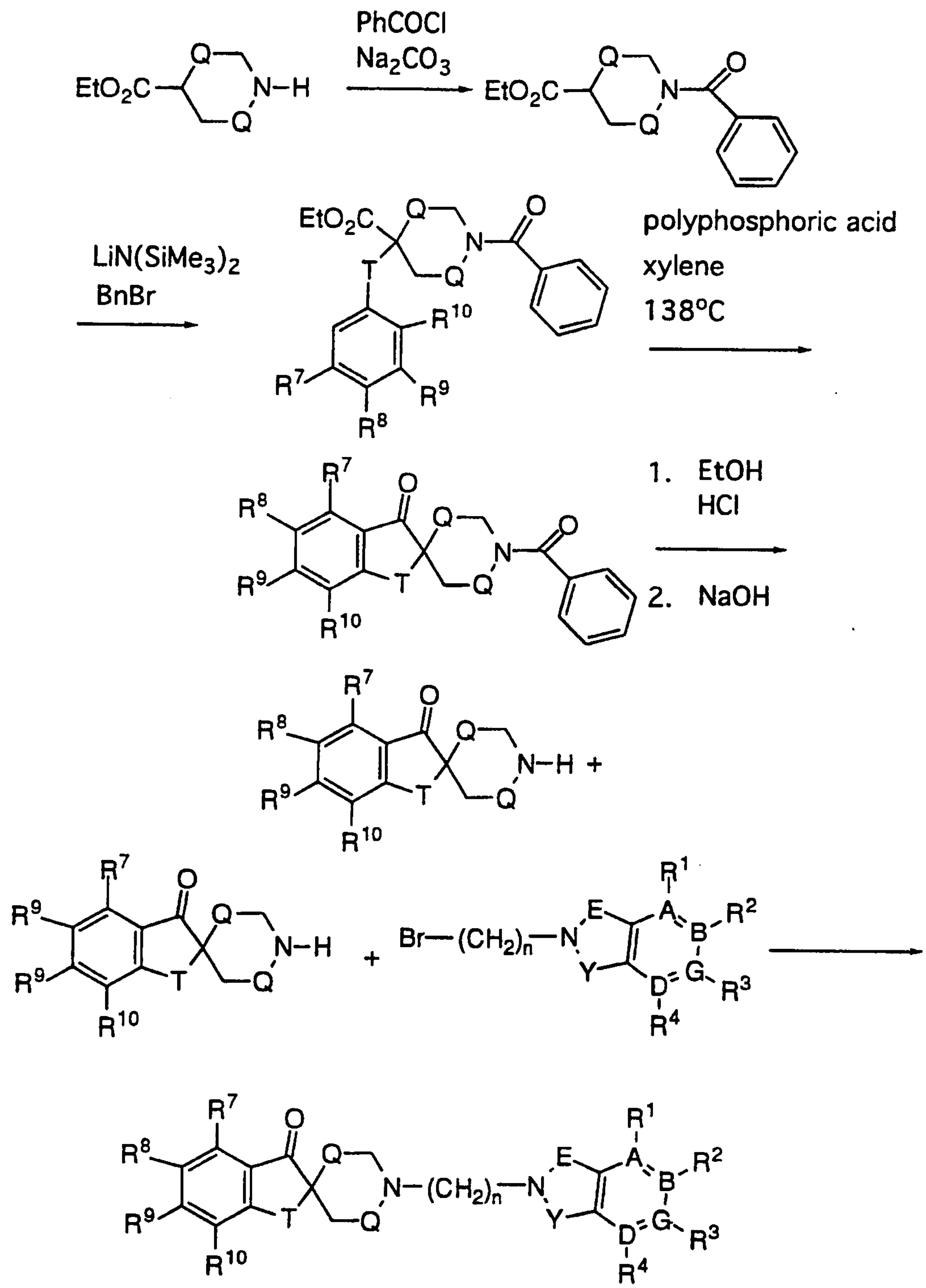


P= benzyl, benzyloxycarbonyl or tert-butoxycarbonyl

R^{11}= NO_2, OH, SH, CH_2OH, H



Scheme 3


PhCOCl
Na_2CO_3
EtO_2C
N–H
LiN(SiMe$_3$)$_2$
BnBr
polyphosphoric acid
xylene
138°C
1. EtOH
HCl
2. NaOH
Br—(CH$_2$)$_n$—N
N–(CH$_2$)$_n$—N

Abbreviations: DMF is dimethylformamide; EtOH is ethanol.

These compounds are administered in dosages effective to antagonize the alpha1C receptor where such treatment is needed, as in BPH and for inhibiting contraction of prostate tissue. For use in medicine, the salts of the compounds of this invention will be pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds according to the invention or of their pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of this invention include acid addition salts which may, for example, be formed by mixing a solution of the compound according to the invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulphuric acid, fumaric acid, maleic acid, succinic acid, acetic acid, benzoic acid, oxalic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid. Furthermore, where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may include alkali metal salts, e.g. sodium or potassium salts; alkaline earth metal salts, e.g. calcium or magnesium salts; and salts formed with suitable organic ligands, e.g. quaternary ammonium salts.

The present invention includes within its scope prodrugs of the compounds of this invention. In general, such prodrugs will be functional derivatives of the compounds of this invention which are readily convertible _in vivo_ into the required compound. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985. Metabolites of these compounds include active species produced upon introduction of compounds of this invention into the biological mileu.

Where the compounds according to the invention have at least one asymmetric centre, they may accordingly exist as enantiomers. Where the compounds according to the invention possess two or more asymmetric centres, they may additionally exist as diastereoisomers. It is to be understood that all such isomers and mixtures thereof are encompassed within the scope of the present invention. Furthermore,

some of the crystalline forms for compounds of the present invention may exist as polymorphs and as such are intended to be included in the present invention. In addition, some of the compounds of the present invention may form solvates with water or common organic solvents. Such solvates are encompassed within the scope of this invention.

Specific compounds within the scope of the present invention include but are not limited to:

1,1-Dioxido-2-(4-(4-(2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one;

1,1-Dioxido-2-(4-(4-(3,4-dihydro-2-oxo-(1*H*)-quinolin-1-yl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one;

1,1-Dioxido-2-(4-(4-(2-oxo-3,1,4-benzoxazinyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one;

1,1-Dioxido-2-(4-(4-(2-oxo-(1H)-quinolin-1-yl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one;

1,1-Dioxido-2-(4-(4-(2-oxo-(1H)-quinolin-1-yl)-piperidin-1-yl)-butyl)-5-nitro-1,2-benzisothiazol-3(2H)-one;

6-Chloro-1,1-dioxido-2-(4-(4-(2-oxo-(1H)-quinolin-1-yl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one;

5-Chloro-1,1-dioxido-2-(4-(4-(2-oxo-(1H)-quinolin-1-yl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one;

1,1-Dioxido-2-(4-(4-(2-oxo-(1H)-quinolin-1-yl)-piperidin-1-yl)-butyl)-7-nitro-1,2-benzisothiazol-3(2H)-one;

1,1-Dioxido-2-(4-(4-(2-oxo-(1H)-quinolin-1-yl)-piperidin-1-yl)-butyl)-4-methoxy-1,2-benzisothiazol-3(2H)-one;

1,1-Dioxido-2-(4-(4-(2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-5-nitro-1,2-benzisothiazol-3(2H)-one;

6-Chloro-1,1-dioxido-2-(4-(4-(2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one;

5-Chloro-1,1-dioxido-2-(4-(4-(2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one;

1,1-Dioxido-2-(4-(4-(2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-7-nitro-1,2-benzisothiazol-3(2H)-one;

1,1-Dioxido-2-(4-(4-(2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-4-methoxy-1,2-benzisothiazol-3(2H)-one;

1,1-Dioxido-2-(4-(4-(5-chloro-2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one;

1,1-Dioxido-2-(4-(4-(3a-(*R*)-8a-(*S*)-2-oxo-3,3a,8,8a-tetrahydro-2H-indeno[1,2-d]oxazolinyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one;

1,1-Dioxido-2-(4-(4-(2-oxonaphth[2,3-d]oxazolinyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one;

1,1-Dioxido-2-(4-(4-(6-methyl-2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one;

1,1-Dioxido-2-(4-(4-(2-oxo-5-phenyl-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one;

1,1-Dioxido-2-(4-(4-(6-methoxy-2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one;

1,1-Dioxido-2-(4-(4-(6-carbomethoxy-2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one;

1,1-Dioxido-2-(4-(4-(5-ethylsulfonyl-2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one;

1,1-Dioxido-2-(4-(4-(2-oxo-3-oxazolo[4,5-b]pyridyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one;

1,1-Dioxido-2-(4-(4-(7-carbethoxy-2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one;

1,1-Dioxido-2-(4-(4-(5-*tert*-butyl-2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one;

1,1-Dioxido-2-(4-(4-(5,7-dimethyl-2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one;

1,1-Dioxido-2-(4-(spiro(1,3-dihydro-1-oxo-2H-indene-2,4'-piperidin-1'-yl)butyl)-1,2-benzisothiazol-3(2H)-one;

1,1-Dioxido-2-(4-(4'-(3,4-dihydro-1-oxonapththalene)-2(1H)-spiropiperidin-1'-yl)butyl)-1,2-benzisothiazol-3(2H)-one;

4-(3,4-Dihydro-6-methyl-spiro[2H-1-benzopyran-2,4'-piperidine-4(3H)-one]-1'-yl)-butylphthalimide;

4-(Spiro(piperidine-4,6'-[6H]thieno[2,3-b]thiopyran-4'(5'H)-one-1'-yl)-butylphthalimide;

4-(Spiro[benzothiazol-2(3H),4'-piperidin-1'-yl)-butylphthalimide;

4-(3,4-Dihydro-6-methoxy-spiro[2H-1-benzopyran-2,4'-piperidine-4(3H)-one]-1'-yl)-butylphthalimide;

4-(3,4-Dihydro-6-methanesulfonylamidyl-spiro[2H-1-benzopyran-2,4'-piperidine-4(3H)-one]-1'-yl)-butylphthalimide;

1,1-Dioxido-2-(4-(spiro[benzothiazol-2(3H),4'-piperidin-1'-yl)-butyl)-1,2-benzisothiazol-3(2H)-one;

4-(6-Trifluoromethyl-spiro[benzothiazol-2(3H),4'-piperidin-1'-yl)-butylphthalimide;

1,1-Dioxido-2-(4-(spiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-butyl)-1,2-benzisothiazol-3(2H)-one;

4-(Spiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-butylphthalimide;

4-(Spiro[2H-1,3-benzoxazine-2,4'-piperidin]-1'-yl)-butylphthalimide;

3,3-Dioxido-1,2-dehydro-2-(4-(spiro[2H-indene-2,4'-piperidine-1(3H)-one]-1'-yl)-butyl)-naphth[1,2-d]isothiazol-1-one;

1,1-Dioxido-2-(4-(spiro[2H-indene-2,4'-piperidine-1(3H)-one]-1'-yl)-butyl)-4-methoxy-1,2-benzisothiazol-3(2H)-one;

1,1-Dioxido-2-(4-(spiro[2H-indene-2,4'-piperidine-1(3H)-one]-1'-yl)-butyl)-7-methoxy-1,2-benzisothiazol-3(2H)-one;

1,1-Dioxido-2-(4-(spiro(1,3-dihydro-1-oxo-2H-indene-2,4'-piperidin-1'-yl)butyl)-5-methoxy-1,2-benzisothiazol-3(2H)-one;

1,1-Dioxido-2-(4-(spiro(1,3-dihydro-1-oxo-2H-indene-2,4'-piperidin-1'-yl)butyl)-6-methoxy-1,2-benzisothiazol-3(2H)-one;

1,1-Dioxido-2-(4-(spiro(1,3-dihydro-1-oxo-2H-indene-2,4'-piperidin-1'-yl)butyl)-5-methyl-1,2-benzisothiazol-3(2H)-one;

1,1-Dioxido-2-(4-(spiro(1,3-dihydro-1-oxo-2H-indene-2,4'-piperidin-1'-yl)butyl)-5-chloro-1,2-benzisothiazol-3(2H)-one;

1,1-Dioxido-2-(4-(spiro(1,3-dihydro-1-oxo-2H-indene-2,4'-piperidin-1'-yl)butyl)-5-fluoro-1,2-benzisothiazol-3(2H)-one;

1,1-Dioxido-2-(4-(spiro(1,3-dihydro-1-oxo-2H-indene-2,4'-piperidin-1'-yl)butyl)-5-nitro-1,2-benzisothiazol-3(2H)-one;

1,1-Dioxido-2-(4-(spiro(1,3-dihydro-1-oxo-2H-indene-2,4'-piperidin-1'-yl)butyl)-6-nitro-1,2-benzisothiazol-3(2H)-one;

1,1-Dioxido-2-(4-(spiro(1,3-dihydro-1-oxo-2H-indene-2,4'-piperidin-1'-yl)butyl)-isothiazolo[5,4-c]pyridin-3(2H)-one;

1,1-Dioxido-2-(4-(spiro(1,3-dihydro-1-oxo-2H-indene-2,4'-piperidin-1'-yl)butyl)-isothiazolo[5,4-b]pyridin-3(2H)-one ;

1,1-Dioxido-2-(4-(4-(6-methyl-2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-5-nitro-1,2-benzisothiazol-3(2H)-one;

2-(4-(Spiro(1,3-dihydro-1-oxo-2H-indene-2,4'-piperidin-1'-yl)butyl)-pyrrolo[3,4b]pyridin-5,7(1H)-dione;

1,1-Dioxido-2,3-dihydro-2-(4-(spiro[2H-indene-2,4'-piperidine-1(3H)-one]-1'-yl)-butyl)-naphth[1,8-de]isothiazin-3-one; and

1,1-Dioxido-2-(4-(spiro[3-oxo-phthalan-1,4'-piperidin-1'-yl)butyl)-1,2-benzisothiazol-3(2H)-one;

1,1-Dioxido-2-(4-(4-(1,3-dihydro-2-oxo-2H-benzimidazolin-1-yl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one;

1,1-Dioxido-2-(4-(4-(1,3-dihydro-2-oxo-3-methyl-2H-benzimidazolin-1-yl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one;

1,1-Dioxido-2-(4-(4-(1,3-dihydro-2-oxo-5-methyl-2H-benzimidazolin-1-yl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one;

1,1-Dioxido-2-(4-(4-(1,3-dihydro-2-oxo-4-methyl-2H-benzimidazolin-1-yl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one;

1,1-Dioxido-2-(4-(4-(1,3-dihydro-2-oxo-5-methoxy-2H-benzimidazolin-1-yl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one;

1,1-Dioxido-2-(4-(4-(1,3-dihydro-2-oxo-5-chloro-2H-benzimidazolin-1-yl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one;

1,1-Dioxido-2-(4-(4-(1,3-dihydro-2-oxo-5-fluoro-2H-benzimidazolin-1-yl)-piperidin-1-yl)-butyl)-5-chloro-1,2-benzisothiazol-3(2H)-one;

1,1-Dioxido-2-(4-(4-(1,3-dihydro-2-oxo-5-methyl-2H-benzimidazolin-1-yl)-piperidin-1-yl)-butyl)-5-chloro-1,2-benzisothiazol-3(2H)-one;

1,1-Dioxido-2-(4-(4-(1,3-dihydro-2-oxo-6-methyl-2H-benzimidazolin-1-yl)-piperidin-1-yl)-butyl)-5-chloro-1,2-benzisothiazol-3(2H)-one;

1,1-Dioxido-2-(4-(4-(5-methyl-2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-5,6-dihydro-[1,4]dioxino[2,3-e]benzisothiazol-3(2H)-one;

1,1-Dioxido-2-(4-(4-(2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-5,6-dihydro-[1,4]dioxino[2,3-e]benzisothiazol-3(2H)-one;

1,1-Dioxido-2-(4-(4-(spiro-1,3-dihydro-1-oxo-2H-indenyl)-2,4'-piperidin-1'-yl)-butyl)-5,6-dihydro-[1,4]dioxino[2,3-e]benzisothiazol-3(2H)-one;

1,1-Dioxido-2-(4-(4-(1,3-dihydro-2-oxo-1H-3,4-dihydroquinazolin-1-yl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one;

2-(4-Hydroxybutyl)-1,1-dioxido-5,6-dihydro-[1,4]dioxino[2,3-d]benzisothiazol-3(2H)-one;

1,1-Dioxido-2-(4-(4-(2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-5-ethoxy-1,2-benzothiazol-3(2H)-one;

1,1-Dioxido-2-(4-(4-(spiro-1,3-dihydro-1-oxo-2H-indenyl)-2,4'-piperidin-1'-yl)-butyl)-5-ethoxy-1,2-benzothiazol-3(2H)-one;

1,1-Dioxido-2-(4-(4-(spiro-1,3-dihydro-1-oxo-2H-indenyl)-2,4'-piperidin-1'-yl)-butyl)-5-ethyl-1,2-benzothiazol-3(2H)-one;

1,1-Dioxido-2-(4-(4-(2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-5-ethyl-1,2-benzothiazol-3(2H)-one;

1,1-Dioxido-2-(4-(4-(spiro-1,3-dihydro-1-oxo-2H-indenyl)-2,4'-piperidin-1'-yl)-butyl)-5-(2-propyl)-1,2-benzothiazol-3(2H)-one;

1,1-Dioxido-2-(4-(4-(2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-5-(2-propyl)-1,2-benzothiazol-3(2H)-one;

1,1-Dioxido-2-(4-(4-(2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-6-nitro-1,2-benzisothiazol-3(2H)-one;

1,1-Dioxido-2-(4-(4-(2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-5-fluoro-1,2-benzisothiazol-3(2H)-one;

1,1-Dioxido-2-(4-(4-(2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-5-methyl-1,2-benzisothiazol-3(2H)-one;

1,1-Dioxido-2-(4-(4-(2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-5-bromo-1,2-benzisothiazol-3(2H)-one;

1,1-Dioxido-2-(4-(4-(2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-5-trifluoromethyl-1,2-benzisothiazol-3(2H)-one;

1,1-Dioxido-2-(4-(4-(2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-5-trifluoromethoxy-1,2-benzisothiazol-3(2H)-one;

1,1-Dioxido-2-(4-(4-(2-oxo-1-naphth[1,2-d]oxazolinyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one;

1,1-Dioxido-2-(4-(4-(5,6,7,8-tetrahydro-2-oxo-3-naphth[2,3-d]oxazolinyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one;
1,1-Dioxido-2-(4-(4-(5-methyl-2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one;
1,1-Dioxido-2-(4-(4-(5-carbomethoxy-2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one;
1,1-Dioxido-2-(4-(4-(6-fluoro-2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one;
1,1-Dioxido-2-(4-(4-(4-methyl-2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one;
1,1-Dioxido-2-(4-(4-(4-methoxy-2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one;
5-Chloro-1,1-dioxido-2-(4-(4-(6-methyl-2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one;
5-Methylthio-1,1-dioxido-2-(4-(4-(6-methyl-2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one;
5-Ethoxy-1,1-dioxido-2-(4-(4-(6-methyl-2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one;
5-Chloro-1,1-dioxido-2-(4-(4-(6-fluoro-2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one;
4-Methyl-1,1-dioxido-2-(4-(4-(2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one;
4-Chloro-1,1-dioxido-2-(4-(4-(2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one;
4-Ethoxy-1,1-dioxido-2-(4-(4-(2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one;
4-(2-Propyloxy)-1,1-dioxido-2-(4-(4-(2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one;
5-Methoxy-1,1-dioxido-2-(4-(4-(6-methyl-2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one;
1,1-Dioxido-2-(4-(4-(2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-6-methylsulfonyl-1,2-benzisothiazol-3(2H)-one;
5-Methoxy-1,1-dioxido-2-(4-(4-(2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one;

1,1-Dioxido-2-(4-(4-(2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-5-methylsulfonyl-1,2-benzisothiazol-3(2H)-one;
5-Methylthio-1,1-dioxido-2-(4-(4-(2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one;
5-Methylsulfonyl-1,1-dioxido-2-(4-(4-(6-methyl-2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one; or
1,1-Dioxido-2-(4-(4-(2-oxo-1-oxazolo[5,4-b]pyridyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one;
and pharmaceutically acceptable salts, metabolites and prodrugs thereof.

Preferred compounds of the present invention include:
1,1-Dioxido-2-(4-(4-(1,3-dihydro-2-oxo-2H-benzimidazolin-1-yl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one;
1,1-Dioxido-2-(4-(4-(1,3-dihydro-2-oxo-3-methyl-2H-benzimidazolin-1-yl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one;
1,1-Dioxido-2-(4-(4-(1,3-dihydro-2-oxo-5-methyl-2H-benzimidazolin-1-yl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one;
1,1-Dioxido-2-(4-(4-(1,3-dihydro-2-oxo-5-chloro-2H-benzimidazolin-1-yl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one;
1,1-Dioxido-2-(4-(4-(1,3-dihydro-2-oxo-5-fluoro-2H-benzimidazolin-1-yl)-piperidin-1-yl)-butyl)-5-chloro-1,2-benzisothiazol-3(2H)-one;
1,1-Dioxido-2-(4-(4-(1,3-dihydro-2-oxo-5-methyl-2H-benzimidazolin-1-yl)-piperidin-1-yl)-butyl)-5-chloro-1,2-benzisothiazol-3(2H)-one;
1,1-Dioxido-2-(4-(4-(1,3-dihydro-2-oxo-6-methyl-2H-benzimidazolin-1-yl)-piperidin-1-yl)-butyl)-5-chloro-1,2-benzisothiazol-3(2H)-one;
and
1,1-Dioxido-2-(4-(4-(5-methyl-2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-5,6-dihydro-[1,4]dioxino[2,3-e]benzisothiazol-3(2H)-one;
and pharmaceutically acceptable salts, metabolites and prodrugs thereof.

The invention also provides pharmaceutical compositions comprising one or more compounds of this invention in association with a pharmaceutically acceptable carrier. Preferably these compositions are in unit dosage forms such as tablets, pills, capsules, powders, granules, sterile parenteral solutions or suspensions, metered aerosol or liquid sprays, drops, ampoules, auto-injector devices or suppositories;

for oral, parenteral, intranasal, sublingual or rectal administration, or for administration by inhalation or insufflation. Alternatively, the compositions may be presented in a form suitable for once-weekly or once-monthly administration; for example, an insoluble salt of the active compound, such as the decanoate salt, may be adapted to provide a depot preparation for intramuscular injection. For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention. The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions, suitably flavoured syrups, aqueous

or oil suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone or gelatin.

In the treatment of BPH, a suitable dosage level is about 0.01 to 250 mg/kg per day, preferably about 0.05 to 100 mg/kg per day, and especially about 0.05 to 5 mg/kg per day. The compounds may be administered on a regimen of 1 to 4 times per day.

Where the above-described processes for the preparation of the compounds according to the invention give rise to mixtures of stereoisomers, these isomers may be separated by conventional techniques such as preparative chromatography. The compounds may be prepared in racemic form, or individual enantiomers may be prepared either by enantiospecific synthesis or by resolution. The compounds may, for example, be resolved into their component enantiomers by standard techniques, such as the formation of diastereomeric pairs by salt formation with an optically active acid, such as (-)-di-p-toluoyl-d-tartaric acid and/or (+)-di-p-toluoyl-l-tartaric acid followed by fractional crystallization and regeneration of the free base. The compounds may also be resolved by formation of diastereomeric esters or amides, followed by chromatographic separation and removal of the chiral auxiliary.

During any of the above synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in Protective Groups in Organic Chemistry, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene & P.G.M. Wuts, Protective Groups in Organic Synthesis, John Wiley & Sons, 1991. The protecting groups may be removed at a convenient subsequent stage using methods known from the art.

The specificty of binding of compounds showing affinity for the α1C receptor is shown by comparing affinity to membranes obtained from COS cells tranfected with the cloned α1C receptor and membranes from tissues known to express other types of alpha or beta adrenergic receptors. In addition, the cloned human α1A and a hybrid human/rat α1B (with only the cytoplasmic, carboxy terminal region being rat sequence) could be used for this purpose, along with the human α1C receptor expressed in COS cells . Expression of the cloned human α1A, α1B, and α1C receptors and comparison of their binding properties with known selective antagonists provides a rational way for selection of compounds and discovery of new compounds with predictable pharmacological activities. Antagonism by these compounds of the human alpha1C adrenergic receptor subtype may be functionally demonstrated in anesthetized animals. These compounds may be used to increase urine flow without exhibiting orthostatic hypotensive effects.

The human alpha adrenergic receptor of the 1-C subtype was identified, cloned and expressed. A partial coding region for this receptor was generated by reverse transcriptase-polymerase chain reaction technology, RT-PCR. Accordingly, degenerate oligonucleotides encoding amino acids conserved in the fifth and sixth transmembrane domains of all three α1 receptor subtypes (A, B, C) were used to prime RT-PCR reactions using human heart mRNA as template. The predicted sized products were cloned and sequenced. Translation of the amplified cDNA yielded an open reading frame encoding a protein 95% homologous to the bovine α1C receptor (Fig.2, SEQ. ID:5: and SEQ. ID:6:). This partial sequence was used to obtain a larger cDNA clone from a human hippocampus library (Fig. 3, SEQ. ID:6:). The remaining coding region was obtained by PCR amplification of human genomic DNA using primers based on the cDNA sequence and the last six amino acids of bovine α1C receptor (Fig. 4, SEQ.ID:10:). The complete receptor was then assembled using the partial sequences shown in Fig. 3, SEQ.ID:6: and Fig. 4, SEQ. ID:10:, to generate the sequence shown in Fig. 5, SEQ. ID:11:. The translation of this sequence is shown in Fig. 6, SEQ. ID:12:, and the

alignment of the nucleotide and amino acid sequences, and the 5'-untranslated sequences, is shown in Fig. 7, SEQ. ID:11: and SEQ. ID:12:.

The 3'-terminal six amino acids of the human α1C adrenergic receptor were confirmed by screening a human genomic library with the radiolabeled 3'-terminal 512 nucleotides of the SEQ. ID:10: clone previously obtained. A complete human exon 2 was generated in this manner and sequenced. The nucleotide sequence of this gene is provided in figure 19, SEQ. ID:27: and the amino acid sequence is provided in figure 20, SEQ. ID:28:. We discovered that this clone was identical to the original 3'-terminal portion of the gene, except that:

1) There are five silent nucleotide changes between the new clone and the previously obtained clone (the last five codons, including the stop codon, each have a silent change in the third nucleotide); and

2) At nucleotide position 1636 (amino acid 347), there is a cytosine to thymine base change resulting in the formation of a Pst1 site at that location and a concommitant single amino acid change of Arg to Cys. Thus, we have confirmed and localized the site of the two-allele Pst1 restriction fragment polymorphism (RFLP) noted by Hoehe et al., [Human Mol. Genetics, 1(5):349 (8/92)]. Through pharmacological studies using clones of both alleles, we have confirmed that the Arg to Cys change appear to be pharmacologically indistinguishable (see Table II, Example 11, below).

The cloned human α1C receptor, when expressed in mammalian cell lines (see Fig. 8), is used to discover ligands that bind to the receptor and alter its function. In addition, the cloned α1C receptor enables quanititation of mRNA levels in human tissues, including the aorta and prostate, by RNase protection assays. For these purposes, a complete coding sequence of the receptor is provided. However, as long as the ligand binding and signal transduction segments of the receptor (G-protein interaction) are intact, truncation at the 3' end of the sequence does not affect the functioning of the receptor. Thus, in addition to the sequence provided in SEQ. ID:11:, a sequence,

truncated at the 3' end, SEQ. ID:26: is disclosed, which consists entirely of human alpha1C sequence.

Once the human receptor is cloned and expressed in a cell such as COS cells or CHO cells, the receptor is free of other human proteins. The membranes from cells expressing different human alpha adrenergic receptor subtypes are then isolated according to methods well known in the art for membrane associated receptor binding assays. For example, the method of Schwinn, et al., (J. Biol. Chem., 265:8183-8189, 1990) may be used. A compound of interest is used to compete with the binding of a known, quantifiable alpha receptor ligand. Thus, radiolabled prazosin, niguldipine, 5-methyl urapidil, terazosin, dozazosin, phenoxybenzamine, WB4101, benoxathian, HEAT (2-[ß-(4-hydroxy-3-iodophenyl)ethylaminomethyl]tetralone, or phentolamine may be used for this purpose (see, for example, Robert R. Ruffolo, Jr., α-Adrenoreceptors: Molecular Biology, Biochemistry and Pharmacology, (Progress in Basic and Clinical Pharmacology series, Karger, 1991), page 29). Because of the ease of ^{125}Iodine detection, ^{125}I-HEAT may be preferred for this purpose. By increasing the amount of unlabeled, test compound, the labeled compound is competed off the receptor. From these experiments, IC_{50} values for each test compound and receptor subtype is determined.

A new sequence for the human α1A adrenergic receptor which is more homologous to the rat α1A adrenergic receptor sequence is also provided herein (see Example 12 and figures 22, 23, and 24, SEQ. ID:29: and SEQ. ID:30:). While no difference in ligand binding has thus far been observed based on the different amino terminal amino acid sequences between these two receptors, such differences cannot be ruled out except by screening compounds against both clones. Since a new human α1A adrenergic receptor sequence is provided herein, compounds identified using the earlier reported human α1A adrenergic receptor sequence can now be confirmed against this clone.

Compounds of this invention exhibiting selective human α1C adrenergic receptor antagonism may further be defined by counterscreening. This is accomplished according to methods known in

the art using other receptors responsible for mediating diverse biological functions. Compounds which are both selective amongst the various human alpha1 adrenergic receptor subtypes and which have low affinity for other receptors, such as the alpha2 adrenergic receptors, the ß-adrenergic receptors, the muscarinic receptors, the serotonin receptors, and others are particularly preferred. The absence of these non-specific activities may be confirmed by using cloned and expressed receptors in an analogous fashion to the method disclosed herein for identifying compounds which have high affinity for the various huaman alpha1 adrenergic receptors. Furthermore, functional biological tests are used to confirm the effects of identified compounds as alpha1C adrenergic receptor antagonists.

Compounds of this patent disclosure may be used alone at appropriate dosages defined by routine testing in order to obtain optimal antagonism of the human $\alpha 1C$ adrenergic receptor while minimizing any potential toxicity. In addition, co-administration or sequential administration of other agents which alleviate the effects of BPH is desirable. Thus, in one embodiment, this includes administration of compounds of this invention and a human testosterone 5-α reductase inhibitor. Included in this embodiment are inhibitors of 5-alpha reductase isoenzyme 2. Many such compounds are now well known in the art and include such compounds as PROSCAR®, (also known as finasteride, a 4-Aza-steroid; see US Patents 4,377,584 and 4,760,071, for example, hereby incorporated by reference). In addition to PROSCAR®, which is principally active in prostatic tissue due to its selectivity for human 5-α reductase isozyme 2, combinations of compounds which are specifically active in inhibiting testosterone 5-alpha reductase isozyme 1 (found particularly in skin) and compounds which act as dual inhibitors of both isozymes 1 and 2, are useful in combination with compounds of this invention. Compounds that are active as 5α-reductase inhibitors have been described in WO93/23420, EP 0572166; WO 93/23050; WO93/23038, ; WO93/23048; WO93/23041; WO93/23040; WO93/23039; WO93/23376;

WO93/23419, EP 0572165; WO93/23051, each of which is hereby incorporated by reference.

The present invention also has the objective of providing suitable topical, oral, systemic and parenteral pharmaceutical formulations for use in the novel methods of treatment of the present invention. The compositions containing compounds of this invention as the active ingredient for use in the specific antagonism of human alpha1C adrenergic receptors can be administered in a wide variety of therapeutic dosage forms in conventional vehicles for systemic administration. For example, the compounds can be administered in such oral dosage forms as tablets, capsules (each including timed release and sustained release formulations), pills, powders, granules, elixirs, tinctures, solutions, suspensions, syrups and emulsions, or by injection. Likewise, they may also be administered in intravenous (both bolus and infusion), intraperitoneal, subcutaneous, topical with or without occlusion, or intramuscular form, all using forms well known to those of ordinary skill in the pharmaceutical arts. An effective but non-toxic amount of the compound desired can be employed as an alpha1C antagonistic agent.

The daily dosage of the products may be varied over a wide range from 0.01 to 1,000 mg per adult human/per day. For oral administration, the compositions are preferably provided in the form of scored or unscored tablets containing 0.01, 0.05, 0.1, 0.5, 1.0, 2.5, 5.0, 10.0, 15.0, 25.0, and 50.0 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. An effective amount of the drug is ordinarily supplied at a dosage level of from about 0.0002 mg./kg to about 50 mg./kg. of body weight per day. The range is more particularly from about 0.001 mg./kg to 7 mg./kg. of body weight per day. With reference to terazosin, it is predictable that the potent and more selective compounds of this invention are effective at doses equal to or between ten and a hundred fold lower than dosages utilized for that compound (see, for example, US Patent 5,212,176). The dosages of the alpha1C adrenergic receptor and testosterone 5-alpha

reductase inhibitors are adjusted when combined to achieve desired effects. As those skilled in the art will appreciate, less 5-alpha reductase inhibitor may be required when the acute symptoms of BPH are alleviated by treatment with the alpha1C adrenergic receptor inhibitor of this invention. On the other hand, dosages of these various agents may be independently optimized and combined to achieve a synergistic result wherein the pathology is reduced more than it would be if either agent were used alone.

The term "therapeutically effective amount" as used herein means that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue, system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician, which includes alleviation of the symptoms of the disease being treated. The term inhibitorily effective amount or antagonistically effective amount as used herein means that amount of an active compound which, when contacted with a particular enzyme or receptor, interrupts the usual catalytic activity or signal transduction of that enzyme or receptor.

The term "subject," as used herein refers to an animal, preferably a mammal, most preferably a human, who has been the object of treatment, observation or experiment.

Advantageously, compounds of the present invention may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three or four times daily. Furthermore, compounds for the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in that art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

For the treatment of benign prostatic hyperplasia, prostatitis and the prevention and/or treatment of prostatic cancer, compounds of this invention exhibiting alpha1C adrenergic receptor

blockade can be combined with a therapeutically effective amount of a 5α-reductase 2 inhibitor, such as finasteride, in addition to a 5α-reductase 1 inhibitor, such as 4,7ß-dimethyl-4-aza-5α-cholestan-3-one, in a single oral, systemic, or parenteral pharmaceutical dosage formulation. Alternatively, a combined therapy can be employed wherein the alpha1C adrenergic receptor antagonist and the 5α-reductase 1 or 2 inhibitor are administered in separate oral, systemic, or parenteral dosage formulations. See, e.g., U.S. Patent No.'s 4,377,584 and 4,760,071 which describe dosages and formulations for 5α-reductase inhibitors.

For combination treatment with more than one active agent, where the active agents are in separate dosage formulations, the active agents can be administered concurrently, or they each can be administered at separately staggered times.

The dosage regimen utilizing the compounds of the present invention is selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; the renal and hepatic function of the patient; and the particular compound thereof employed. A physician or veterinarian of ordinary skill can readily determine and prescribe the effective amount of the drug required to prevent, counter or arrest the progress of the condition. Optimal precision in achieving concentration of drug within the range that yields efficacy without toxicity requires a regimen based on the kinetics of the drug's availability to target sites. This involves a consideration of the distribution, equilibrium, and elimination of a drug.

In the methods of the present invention, the compounds herein described in detail can form the active ingredient, and are typically administered in admixture with suitable pharmaceutical diluents, excipients or carriers (collectively referred to herein as "carrier" materials) suitably selected with respect to the intended form of administration, that is, oral tablets, capsules, elixirs, syrups

and the like, and consistent with conventional pharmaceutical practices.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents and coloring agents can also be incorporated into the mixture. Suitable binders include, without limitation, starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes and the like. Lubricants used in these dosage forms include, without limitation, sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum and the like.

The liquid forms in suitably flavored suspending or dispersing agents such as the synthetic and natural gums, for example, tragacanth, acacia, methyl-cellulose and the like. Other dispersing agents which may be employed include glycerin and the like. For parenteral administration, sterile suspensions and solutions are desired. Isotonic preparations which generally contain suitable preservatives are employed when intravenous administration is desired.

The compounds of the present invention can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

Compounds of the present invention may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. The compounds of the present invention may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinyl-

pyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamidephenol, polyhydroxy-ethylaspartamidephenol, or polyethyleneoxidepolylysine substituted with palmitoyl residues. Furthermore, the compounds of the present invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydro-pyrans, polycyanoacrylates and cross-linked or amphipathic block copolymers of hydrogels.

Compounds of this invention may be administered in any of the foregoing compositions and according to dosage regimens established in the art whenever specific blockade of the human alpha1C adrenergic receptor is required.

The following examples are provided to further define the invention without, however, limiting the invention to the particulars of these examples.

EXAMPLE 1

PCR amplification, cloning and sequencing of phα1X:

Based on the amino acid homologies of human α1A, rat α1B and bovine α1C receptors, degenerate oligonucleotides were designed to amplify cDNAs encoding all three receptor subtypes. These oligonucleotides are:

WL' (SEQ. ID:1) TTTTCTAGAT TRTTNARRTA NCCNAGCC 28

MYC (SEQ. ID:2) TTTACTAGTA TCSTNGTNAT GTAYTG 16

WC' (SEQ. ID:3) TTTTCTAGAG AARAANGGNA RCCARC 26

Oligonucleotides MYC and WL' were used as primers in a reverse transcription PCR amplification of human heart mRNA (Clontech) using the RNA PCR kit from Perkin Elmer Cetus. Briefly, 0.5 ug of mRNA was reverse transcribed in a volume of 20 ul using either random oligonucleotide primers (reaction 1) or oligo dT primer (reaction 2). Reactions 1 and 2 were pooled and served as template for PCR amplification as follows:

PCR Reactions:

Primary reaction (50 ul)

5 ul 10X buffer from Perkin Elmer Cetus GeneAmp Kit
8 ul 1.25 mM each stock of dATP,dCTP,dGTP, and dTTP
3ul first strand cDNA
1 ul 25 pMoles oligo MYC
1 ul 25 pMoles oligo WL'
0.25 ul 1.25 units Amplitaq DNA polymersase
31.75 ul water

Reaction conditions; 40 cycles of 94^{o}C 1'; 45^{o}C 2'; 72^{o}C 2'

Secondary reaction (100 ul)

9.5 ul 10X buffer from Perkin Elmer Cetus GeneAmp Kit
16ul 1.25 mM each stock of dATP,dCTP,dGTP, and dTTP
5ul first strand cDNA
2 ul 50 pMoles oligo MYC
2 ul 50 pMoles oligo WC'
0.5 ul 2.5 units Amplitaq DNA polymersase
65 ul water

Reaction conditions; 40 cycles of 94^{o}C 1'; 45^{o}C 2'; 72^{o}C 2'

Prep scale tertiary reaction 3 X 200 ul:

19.5 ul	10X buffer
32 ul	1.25 mM each stock of dATP, dCTP, dGTP, and dTTP
5 ul	secondary PCR reaction
4 ul	100 pMoles oligo MYC
4 ul	100 pMoles oligo WC'
1 ul	5 units Amplitaq DNA polymerase
134.5 ul	water

Reaction conditions; 30 cycles of 94°C 1'; 50°C 2'; 72°C 2'

The PCR product was purified by Qiagen spin columns and digested with restriction endonucleases SpeI and XbaI. The fragment was then ligated into SpeI/XbaI cut pGEM9Zf(-). The ligation mix was used to transform E. coli XL-1 blue. Plasmid DNA was isolated from white transformants and sequenced by the dideoxy chain termination method. The base sequence obtained is shown in Fig. 1, SEQ. ID:4:.

EXAMPLE 2

Isolation of partial alpha1C cDNA Clone:

A cDNA library prepared from mRNA isolated from human hippocampus (Stratagene) was screened by plaque hybridization using phα1X as a probe. Hybridization conditions were as follows:

5XSSC (1XSSC is 0.15M sodium chloride, 0.015M sodium citrate,
50% Formamide
5X Denhardt's Solution (1% Ficoll, 1% polyvinylpyrrolidone, 1% bovine serum albumin)
0.15 mg/ml salmon sperm DNA
hybridize overnight at 42° C.

Filters were washed 3 times in 2XSSC, 0.1% SDS at room temperature for 5', then 1 time in 1XSSC, 0.1% SDS at 50C for 30'. Positive clones were identified by autoradiography. Phagemid DNA was rescued from the positive plaques and sequenced by the dideoxy chain termination method. The base sequence obtained is shown in Fig. 3, SEQ. ID:7:.

EXAMPLE 3

PCR amplification, cloning and sequencing of 3'CG of alpha1C:

The 3' end of the coding region of human alpha1C adrenergic receptor was amplified from human genomic DNA using two oligonucleotides:

S3C (SEQ ID:8:)

5' TTTGAATTCT GATTTCAAGC CCTCTG 3'

and

3'C (SEQ ID:9:)

5' TTTGAATTCT TANACYTCYT CNCCRTTYTC 3'

as follows:

10 ul 10X buffer from Perkin Elmer Cetus GeneAmp Kit
16 ul 1.25 mM each stock of dATP,dCTP,dGTP, and dTTP
6 ul 1 ug human genomic DNA (Promega)
2 ul 50 pMoles oligo S3C
2 ul 50 pMoles oligo 3'C
0.5 ul 2.5 units Amplitaq DNA polymersase
63.5 ul water

Reaction conditions; 40 cycles of 94°C 1'; 50°C 2'; 72°C 2'

The PCR product was purified by Qiagen spin columns and digested with restriction endonuclease EcoRI. The fragment was then ligated into EcoRI cut pGEM3Zf(-). The ligation mix was used to transform E. coli XL-1 blue. Plasmid DNA was isolated from white transformants and sequenced by the dideoxy chain termination method. The base sequence is shown in Fig. 4, SEQ. ID:10:.

EXAMPLE 4

Assembly of complete coding region of human alpha1c adrenergic receptor:

The complete coding region of human alpha1c adrenergic receptor was assembled by ligating the cDNA clone (see Example 2, figure 3, SEQ ID:7:) and 3'CG (see Example 3, figure 4, SEQ ID:10:) at their common PvuII site (1552-1557 of figure 3, SEQ ID:7: and 59-64 of figure 4, SEQ ID:10:). The complete nucleotide sequence is shown in figure 5, SEQ ID:11:. The amino acid sequence is shown in figure 6, SEQ. ID:12:. Figure 7 shows the structure of the cDNA, including the 5'-untranslated sequences. The very 3' twenty seven nucleotides (6 amino acids) shown is the sequence of the PCR primer used to generate the sequence. However, the function of the receptor, both for ligand binding and signal transduction depends on sequences far removed from the carboxy terminus of the receptor. A completely human sequence is shown in figure 18, SEQ. ID:26: which is truncated at the 3' terimuns.

EXAMPLE 5

Expression of the cloned alpha1C adrenergic receptor:

The complete sequence (SEQ ID:11:) of the human alpha1C adrenergic receptor was subcloned into the eukaryotic expression vector pcDNAI-neo (Invitrogen). The resulting plasmid was transfected into COS-7 cells by electroporation. Cells were harvested after 72 hours and the membranes containing the expressed receptor protein were prepared as described in Schwinn, et al., J. Biol. Chem., 265:8183-8189, 1990. Membranes (5-25 ug, see figure 8) prepared from the COS-7 cells transfected with the vector containing the alpha1C receptor gene specifically bound the alpha 1 antagonist [^{125} I]-HEAT; membranes prepared from the COS-7 cells transfected with the vector alone did not bind the alpha 1 antagonist [^{125} I]-HEAT (figure 8), proving the expression of the alpha1C adrenergic receptor. Binding reactions (total volume = 200 ul) contained 50 mM Tris-HCl pH. 7.4, 5 mM EDTA, 150 mM NaCl, 100 pM [^{125} I]-HEAT, and membranes prepared from COS-7 cells transfected with expression plasmids. Reactions were incubated at room temperature for one hour with shaking. Reactions were filtered onto Whatman GF/C glass fiber filters with a Brandel cell harvester. Filters were washed three times with ice cold buffer and bound radioactivity was determined. Non specific binding was determined in the presence of 10 uM prazosin.

EXAMPLE 6

Screening assay: Alpha 1 C Adrenergic Receptor Binding

Membranes prepared from the transfected COS-7 cells may also be used to identify compounds that bind to the human alpha1C adrenergic receptor. These competition binding reactions (total volume = 200 ul) contain 50 mM Tris-HCl pH. 7.4, 5 mM EDTA, 150 mM NaCl, 100 pM [^{125} I]-HEAT, membranes prepared from COS-7 cells transfected with the alpha1C expression plasmid and increasing amounts of unlabeled ligand. Reactions are incubated at room temperature for one hour with shaking. Reactions were filtered onto Whatman GF/C glass fiber filters with a Brandel cell harvester. Filters were washed three times with ice cold buffer and bound radioactivity was determined. Binding data were analyzed and IC50s determined by an iterative curve fitting program. Results are shown in Figure 9.

EXAMPLE 7

Expression of human alpha1A adrenergic receptor:

The complete coding region for the human alpha1A adrenergic receptor (Bruno, et al., BBRC., 179:1485-1490, (1991); see figure 10, SEQ. ID:13: and figure 11, SEQ. ID:14: herein) was subcloned into the eukaryotic expression vector pcDNAI-neo (Invitrogen). The resulting plasmid was transfected into COS-7 cells by electroporation. Cells were harvested after 72 hours and the membranes containing the expressed receptor protein were prepared as described in Schwinn, et al., J. Biol. Chem., 265:8183-8189, 1990. Membranes prepared from the COS-7 cells transfected with the vector containing the alpha1A receptor gene specifically bound the alpha 1 antagonist [^{125} I]-HEAT; membranes prepared from the COS-7 cells transfected with the vector alone did not bind the alpha 1 antagonist [^{125} I]-HEAT.

Binding reactions (total volume = 200 ul) contained 50 mM Tris-HCl pH. 7.4, 5 mM EDTA, 150 mM NaCl, 100 pM [^{125}I]-HEAT, and membranes prepared from COS-7 cells transfected with expression plasmids. Reactions are incubated at room temperature for one hour with shaking. Reactions were filtered onto Whatman GF/C glass fiber filters with a Brandel cell harvester. Filters were washed three times with ice cold buffer and bound radioactivity was determined. Non-specific binding was determined in the presence of 10 uM prazosin.

EXAMPLE 8

Expression of human alpha1B adrenergic receptor:

1. PCR amplification of partial cDNA for human alpha1B adrenergic receptor:

Amplification of 5XB clones

5XB, SEQ. ID:15: 5' TCT AGA CCA TGA AYC CNG AYC TGG 3'

A1B, SEQ. ID:16: 5' TTT GAA TTC ACA TWC CGA CYA CAA TGC CC 3'

Oligonucleotides 5XB and A1B were used as primers in a reverse transcription PCR amplification of human heart mRNA (Clontech) using the Invitrogen Copy Kit. Briefly, 1.0 ug of mRNA was reverse transcribed in a volume of 20 ul using oligonuleotide WC' as primer.

Primary reaction (50 ul)
- 5 ul 10X buffer from Perkin Elmer Cetus GeneAmp Kit
- 8 ul 1.25 mM each stock of dATP,dCTP,dGTP, and dTTP

2.5 ul first strand cDNA
1 ul 25 pMoles oligo 5XB
1 ul 25 pMoles oligo A1B
0.25 ul 1.25 units Amplitaq DNA polymersase
32.75 ul water

Reaction conditions; 40 cycles of 94°C 1'; 58°C 2'; 72°C 2'

The PCR product was directly ligated into pCR vector (Invitrogen) and used to transform E. coli INVαF' (Invitrogen). Plasmid DNA was isolated from white transformants and sequenced by the dideoxy chain termination method. The base sequence is shown in Fig. 12, SEQ. ID:17:

2. Amplification of EFK clones

EFK, SEQ. ID:18: 5' GAAGGCGCGCTTGAACTC 3'

5B1, SEQ. ID:19: 5' AGAGAACCACCAAGAACC 3'

Oligonucleotides EFK and 5B1 were used as primers in a reverse transcription PCR amplification of human aorta mRNA (Clontech) using the Invitrogen Copy Kit. Briefly, 1.0 ug of mRNA was reverse transcribed in a volume of 20 ul using oligo dT as primer.

Primary reaction (50 ul)
5 ul 10X buffer from Perkin Elmer Cetus GeneAmp Kit
8 ul 1.25 mM each stock of dATP,dCTP,dGTP, and dTTP
2.0 ul first strand cDNA
1 ul 25 pMoles oligo EFK
1 ul 25 pMoles oligo 5B1

0.25 ul 1.25 units Amplitaq DNA polymersase
33.25 ul water

Reaction conditions; 40 cycles of 94°C 1'; 58°C 2'; 72°C 2'

The PCR product was directly ligated into pCR vector (Invitrogen) and used to transform E. coli INVaF' (Invitrogen). Plasmid DNA was isolated from white transformants and sequenced by the dideoxy chain termination method. The base sequence is shown in Fig. 13, SEQ. ID:20:.

3. Assembly of partial cDNA for human alpha1B adrenergic receptor

A partial cDNA clone encoding the human alpha1B adrenergic receptor was assembled by joining the 5XB sequence (SEQ. ID:17:) and the EFK sequence (SEQ. ID:20:) at their common BamHI site.

4. Amplification of the 3' end of rat alpha1B adrenergic receptor

S4B, SEQ. ID:21: 5' TTT GAA TTC ATG TTC AAG GTG GTG TTC 3'

3'B2, SEQ. ID:22: 5' TTT GAA TTC TAA AASTGN CCN GGN SCC AGN GGC AT 3'

Oligonucleotides S4B and 3'B2 were used as primers in a reverse transcription PCR amplification of rat heart mRNA using the Invitrogen Copy Kit. Briefly, 0.6 ug of mRNA was reverse transcribed in a volume of 20 ul using oligo dT as primer.

Primary reaction (50 ul)
5 ul 10X buffer from Perkin Elmer Cetus GeneAmp Kit

8 ul 1.25 mM each stock of dATP,dCTP,dGTP, and dTTP
2.0 ul first strand cDNA
1 ul 25 pMoles oligo EFK
1 ul 25 pMoles oligo 5B1
0.25 ul 1.25 units Amplitaq DNA polymersase
33.25 ul water

Reaction conditions; 40 cycles of 94^{o}C 1'; 58^{o}C 2'; 72^{o}C 2'

The PCR product was directly ligated into pCR vector (Invitrogen) and used to transform E. coli INVαF' (Invitrogen). Plasmid DNA was isolated from white transformants and sequenced by the dideoxy chain termination method. The base sequence is shown in Fig. 14, SEQ. ID:23:.

5. Assembly and expression of a functional human/rat hybrid alpha1B adrenergic receptor

The partial human alpha1B adrenergic receptor cDNA was joined to the 3' end of the rat alpha1B adrenergic receptor cDNA at their common BssHII restriction endonuclease site. This composite sequence is shown in figure 15, SEQ. ID:24:, and the amino acid sequence is shown in Fig. 16, SEQ. ID:25:

The complete coding region for the human/rat alpha1B adrenergic receptor was subcloned into the eukaryotic expression vector pcDNAI-neo (Invitrogen). The resulting plasmid was transfected into COS-7 cells by electroporation. Cells were harvested after 72 hours and the membranes containing the expressed receptor protein were prepared as described in Schwinn, et al., J. Biol. Chem., 265:8183-8189, 1990. Membranes prepared from the COS-7 cells transfected with the vector containing the alpha1B receptor gene specifically bound the alpha 1 antagonist [^{125}I]-HEAT; membranes prepared from the COS-7 cells transfected with the vector alone did not bind the alpha 1

antagonist [^{125}I]-HEAT. Binding reactions (total volume = 200 ul) contained 50 mM Tris-HCl pH. 7.4, 5 mM EDTA, 150 mM NaCl, 100 pM [^{125}I]-HEAT, and membranes prepared from COS-7 cells transfected with expression plasmids. Reactions are incubated at room temperature for one hour with shaking. Reactions were filtered onto Whatman GF/C glass fiber filters with a Brandel cell harvester. Filters were washed three times with ice cold buffer and bound radioactivity was determined. Non specific binding was determined in the presence of 10 uM prazosin.

EXAMPLE 9

Selective Binding assays

Membranes prepared from COS-7 cells transfected with the human alpha 1 receptor subtype expression vectors may also be used to identify compounds that selectively bind to the human alpha1C adrenergic receptor. These competition binding reactions (total volume = 200 ul) contain 50 mM Tris-HCl pH. 7.4, 5 mM EDTA, 150 mM NaCl, 100 pM [^{125}I]-HEAT, membranes prepared from COS-7 cells transfected with the respective alpha 1 subtype expression plasmid and increasing amounts of unlabeled ligand. Reactions are incubated at room temperature for one hour with shaking. Reactions were filtered onto Whatman GF/C glass fiber filters with a Brandel cell harvester. Filters were washed three times with ice cold buffer and bound radioactivity was determined. Binding data were analyzed and IC50s determined by an iterative curve fitting program. Table I shows the results from such an analysis.

Compound	IC50 (nM) α1A	α1B	α1C
prazosin	0.6	2.4	1
terazosin	4	5	19
doxazosin	5	2	9
phenoxybenzamine	6.1	4.3	4.0
WB4101	1	16	1
benoxathian	2.5	68	1.5
phentolamine	36	650	14
5-methyl urapidil	42	270	3.5
S(+) niguldipine	130	670	1.4

EXAMPLE 10

IDENTIFICATION AND CLONING OF A NEW ALLELE FOR THE HUMAN ALPHA1-C ADRENERGIC RECEPTOR

Probes:

3'CG: A 525 bps fragment, specific to complete exon.2 of human alpha1c AR, was PCR amplified from human genomic DNA using a sense primer based on the isolated cDNA clone and an antisense primer based on the last six amino acids of bovine alpha1c cDNA. This PCR product was subcloned and confirmed by sequencing (see Example 3, SEQ.ID:10:).

Genomic Library Screening:

Human W138 Fibroblast genomic library synthesized in the Lambda Fix II vector (2×10^6 recombinants; Stratagene,La Jolla, CA) was screened with (3'CG). This probe was labelled with ^{32}P-dCTP (Amersham) by random-primed labelling kit (Boehringer Mannheim,Indianapolis,IN). A Total 800,000 plaques were screened, using duplicate Hybond-N nylone filters (Amersham,UK). Prior to hybridization, filters were denatured (1.5M NaCl+0.5M NaOH), neutralized (1.5M NaCl+ 1M Tris.Cl,pH 8.0) and washed (0.2M Tris.Cl pH 7.5 + 2 SSC), 5' for each. DNA was cross-linked with UV cross-linker (Stratagene,La Jolla,CA). The filters were, then, hybridized in 50% formamide, 5 x SSC(1xSSC= 0.15M NaCl, 0.015M Na citrate, pH7.0), 0.02% polyvinylpyrophosphate, 0.2% Ficoll, 0.2% bovine serum albumin, 150µg of sheared & boiled Salmon sperm DNA, 10^6 cpm of ^{32}P-labelled probe at 42°C for 40hrs. Filters were washed in 0.1x SSC +1% SDS solution at 60°C for 20'. Two more rounds of screening for 20 "positive" plaques/clones with 3'CG probe confirmed two clones for the alpha1C adrenergic receptor, which were named **48.1C** and **53.1C**. Clone **53.1C** was subjected to further analysis/investigation.

Sub-clonning of Exon.2 :

53.1C lambda DNA was amplified by plate lysis method and purified with Qiagen midi-lambda kit (Qiagen,Chatsworth,CA). A 2.6Kb band excised with EcoRI restriction enzyme was identified by Southern analysis using 3'CG probe. This fragment was then subcloned into pGEM3Zf(+) vector.

DNA sequencing:

Nucleotide sequence analysis of DNA in both direction was performed by Sanger chain termination method.

Result and Discussion:

Sequencing analysis of this genomic clone confirmed that clone 53.1c contains sequences for complete exon.2 flanked by an intron at 5'-end. It also revels that there is a nucleotide change from cytosine (C) to thymine(T) at nucleotide position 1636, amino acid position 347. This change creates a PstI site and changes the codon for arginine (Arg) to cystine (Cys). This data differs from the known/published cDNA sequence of the gene. Southern analysis of human genomic DNA confirms the PstI site in the gene/exon.2.

EXAMPLE 11

COMPARATIVE PHARMACOLOGY OF ALPHA1-C ALLELES

We have cloned two genes for the human alpha-1c receptor. The coding regions differ by a single nucleotide. The genes encode either Cys or Arg at amino acid 347 near the C terminus of the receptor. The nucleotide difference lies within a PstI restriction enzyme recognition site thus creating a Restriction Fragment Length Polymorphism (RFLP). The frequency of allele 1 (LRR) is 0.34; allele 2 (LCR) is 0.66 in 83 unrelated individuals (Hoehe et al "A two-allele PstI RFLP for the alpha-1C adrenergic receptor gene" Human Molecular Genetics 1: 349, 1992; Allele I is defined by a 2.1 kb PstI fragment; allele 2 yields two bands of 1.6 and 0.5 kb). Since the amino acid difference occurs within the intracellular tail of the receptor we would not expect any pharmacological differences between the expressed receptors. To investigate the pharmacological profiles of the two allelic forms of the human alpha-1c adrenergic receptor we ligated the genomic exon 2 fragment of allele 2 to a cDNA clone of allele 1 at a common PvuII restriction site. The two allelic forms were transiently expressed in COS-7 cells using pcDNAI/NEO (Invitrogen) expression vector. Competitive inhibition studies performed in the presence of ^{125}I-HEAT with various antagonists showed no significant difference in their pharmacological profiles (Table II):

Table II
COMPARATIVE PHARMACOLOGY OF ALPHA1-C ALLELES

	IC50 (nM)	
	LRR	LCR
phentolamine	15	17
niguldipine	0.8	1.8
prazosin	1.0	0.9
5-methyl urapidi	3.1	4.3
WB4101	0.9	1.0

EXAMPLE 12

CLONING OF A NOVEL ALPHA1-A ADRENERGIC RECEPTOR

A cosmid library containing FG293 cell line genomic DNA in the double-cos vector sCos-1 was screened as follows: The published human α_{1a} receptor cDNA clone (Bruno et al., BBRC, 179:1485-1490 (1991), and see Fig. 10, SEQ.ID:13:) was cloned into the vector pcDNA1 neo to generate the clone pEXαla. Filters containing approximately 200,000 clones were screened by colony hybridization ([Sambrook, *Molecular Cloning*, Cold Spring Harbor Laboratory Press, New York, 1989]) using a mixed exon 1 probe generated by PCR corresponding to α1a (TMD1-3) , α1b (TMD1-5) and α_{1c} (TMD1-5): 25 cycles of 95° C 1'; 52 °C 30 sec; 72 °C 1.5' using 10 ng of pEX α1b, pEX α1c or pEX α1a and 10 pmoles each of primers 5' MET (5' GAATCCCGACCTGGAC), SEQ.ID:31:, and 3' BAM (5'GGATCCTCAGGGTC), SEQ.ID:32:, for α1b, 5' 597 (5' CCATGGTGTTTCTCTCGGG), SEQ.ID:33: and 3' 1219 (5' GACGCGGCAGTACATGAC), SEQ.ID:34: for α1c or 5' 76 (5' GTCATGATGGCTGGGTACTTG), SEQ.ID:35:, for α_{1a} in a 12 μl reaction containing 1.5 μM each unlabelled dNTP and 50 μCi 3000 Ci/mmol α-[^{32}P] dCTP. The filters were incubated with 1 x 10^6 cpm/ml of probe in 5X SSC, 35% Formamide, 0.02% SDS, 0.1 %

lauroyl sarcosine, 2% blocking buffer (Bohrenger Mannheim), at 42 °C for 18 hours. The filters were washed with 2 liters of 0.5X SSC, 0.1% SDS, 55 °C and exposed to Kodak XAR-5 film. Twelve primary positives were picked from master plates and re-screened using the α_{1a}-specific probe. Cosmid DNA was prepared from second round positive clones, digested with endonucleases Eco RI or Hind III and subjected to Southern blot analysis: Fragments were resolved by electrophoresis, and transferred to a nitrocellulose membrane (Bohrenger Mannheim) with 20X SSC (1X SSC = 0.15M Sodium chloride, 0.015M Sodium citrate, pH 7.0) according to the method of Southern ([Southern, 1975 #14]) . The membrane was hybridized, washed and analyzed as described above. Alpha-1a, α_{1b}, and α_{1c} receptor clones were identified by comparison of restriction patterns with genomic southern blots performed with α_{1a}, α_{1b}, or α_{1c} specific probes. A Cosmid containing α_{1a} receptor exon 1 DNA was subjected to restriction digestion by endonuclease Pst I and subjected to southern blot analysis as above using the α_{1a} -specific probe. Two fragments of 2.3 and 1.6 kb were detected and subcloned into the Pst I site of PGEM 3ZF . The presence of the correct 5' terminal sequences in the 2.3 kb fragment was confirmed by sequencing across the junction between inverted repeat and non-repeat sequences. The 5' end of the α_{1a} receptor gene was ligated to the cDNA clone at their common PstI site, see figures 22-24, SEQ.ID:29:, and SEQ.ID:30:.

EXAMPLE 13

EXEMPLARY COUNTERSCREENS

1. Assay Title: Dopamine D2,D4 in vitro screen

Objective of the Assay:

The objective of this assay is to eliminate agents which specifically affect binding of [3H] spiperone to cells expressing human dopamine receptors D2, D3 or D4.

Method:

Modified from VanTol et al (1991); Nature (Vol 350) Pg 610-613.

Frozen pellets containing specific dopamine receptor subtypes stably expressed in clonal cell lines are lysed in 2 ml lysing buffer (10mM Tris-HCl/5mM Mg, pH 7.4). Pellets obtained after centrifuging these membranes (15' at 24,450 rpm) are resuspended in 50mM Tris-HCl pH 7.4 containing EDTA, MgCl[2], KCl, NaCl, CaCl[2] and ascorbate to give a 1 Mg/mL suspension. The assay is initiated by adding 50-75 μg membranes in a total volume of 500 μl containing 0.2 nM [3H]-spiperone. Non-specific binding is defined using 10 μM apomorphine. The assay is terminated after a 2 hour incubation at room temperature by rapid filtration over GF/B filters presoaked in 0.3% PEI, using 50mM Tris-HCl pH 7.4.

2. Assay Title: Serotonin 5HT1a

Objective of the Assay

The objective of this assay is to eliminate agents which specifically affect binding to cloned human 5HT1a receptor

Method:

Modified from Schelegel and Peroutka *Biochemical Pharmacology* 35: 1943-1949 (1986).

Mammalian cells expressing cloned human 5HT1a receptors are lysed in ice-cold 5 mM Tris-HCl , 2 mM EDTA (pH 7.4) and homogenized with a polytron homogenizer. The homogenate is centrifuged at 1000Xg for 30', and then the supernatant is centrifuged again at 38,000Xg for 30'. The binding assay contains 0.25 nM [3H]8-OH-DPAT in 50 mM Tris-HCl, 4 mM CaCl2 and 1mg/ml ascorbate. Non-specific binding is defined using 10 μM propranolol. The assay is terminated after a 1 hour incubation at room temperature by rapid filtration over GF/Cfilters

EXAMPLE 14

EXEMPLARY FUNCTIONAL ASSAYS

In order to confirm the specificity of compounds for the human alpha1C adrenergic receptor and to define the biological activity of the compounds, the following functional tests may be performed:

1. IN VITRO RAT, DOG AND HUMAN PROSTATE AND DOG URETHRA

Taconic Farms Sprague-Dawley male rats, weighing 250-400 grams are sacrificed by cervical dislocation under anesthesia (methohexital; 50 mg/kg, i.p.). An incision is made into the lower abdomen to remove the ventral lobes of the prostate. Each prostate removed from a mongrel dog is cut into 6-8 pieces longitudinally along the urethra opening and stored in ice-cold oxygenated Krebs solution overnight before use if necessary. Dog urethra proximal to prostate is cut into approximately 5 mm rings, the rings are then cut open for contractile measurement of circular muscles. Human prostate chips from transurethral surgery of benign prostate hyperplasia are also stored overnight in ice-cold Krebs solution if needed.

The tissue is placed in a Petri dish containing oxygenated Krebs solution [NaCl, 118 mM; KCl, 4.7 mM; $CaCl_2$, 2.5 mM; KH_2PO_4, 1.2 mM; $MgSO_4$, 1.2 mM; $NaHCO_3$, 2.0 mM; dextrose, 11 mM] warmed to 37°C. Excess lipid material and connective tissue are carefully removed. Tissue segments are attached to glass tissue holders with 4-0 surgical silk and placed in a 5 ml jacketed tissue bath containing Krebs buffer at 37°C, bubbled with 5% CO_2/95% O_2. The tissues are connected to a Statham-Gould force transducer; 1 gram (rat, human) or 1.5 gram (dog) of tension is applied and the tissues are allowed to equilibrate for one hour. Contractions are recorded on a Hewlett-Packard 7700 series strip chart recorder.

After a single priming dose of 3 μM (for rat), 10 μM (for dog) and 20 μM (for human) of phenylephrine, a cumulative

concentration response curve to an agonist is generated; the tissues are washed every 10 minutes for one hour. Vehicle or antagonist is added to the bath and allowed to incubate for one hour, then another cumulative concentration response curve to the agonist is generated.

EC_{50} values are calculated for each group using GraphPad Inplot software. pA_2 ($-\log K_b$) values were obtained from Schild plot when three or more concentrations were tested. When less than three concentrations of antagonist are tested, K_b values are calculated according to the following formula $K_b = \frac{[B]}{x-1}$,

where x is the ratio of EC_{50} of agonist in the presence and absence of antagonist and [B] is the antagonist concentration.

2. MEASUREMENT OF INTRA-URETHRAL PRESSURE IN ANESTHETIZED DOGS

PURPOSE: Benign prostatic hyperplasia causes decreased urine flow rate that may be produced by both passive physical obstruction of the prostatic urethra from increased prostate mass as well as active obstruction due to prostatic contraction. Alpha adrenergic receptor antagonists such as prazosin and terazosin prevent active prostatic contraction, thus improve urine flow rate and provide symptomatic relief in man. However, these are non-selective alpha-1 receptor antagonists which also have pronounced vascular effects. Because we have identified the alpha-1C receptor subtype as the predominent subtype in the human prostate, it is now possible to specifically target this receptor to inhibit prostatic contraction without concomitant changes in the vasculature. The following model is used to measure adrenergically mediated changes in intra-urethral pressure and arterial pressure in anesthetized dogs in order to evaluate the efficacy and potency of selective alpha adrenergic receptor antagonists. The goals are to: 1) identify the alpha-1 receptor subtypes responsible for prostatic/urethral contraction and vascular responses, and 2) use this model to evaluate novel selective alpha adrenergic antagonists. Novel

and standard alpha adrenergic antagonists may be evaluated in this manner.

METHODS: Male mongrel dogs (7-12 kg) are used in this study. The dogs are anesthetized with pentobarbital sodium (35 mg/kg, i.v. plus 4 mg/kg/hr iv infusion). An endotracheal tube is inserted and the animal ventilated with room air using a Harvard instruments positive displacement large animal ventilator. Catheters (PE 240 or 260) are placed in the aorta via the femoral artery and vena cava via the femoral veins (2 catheters, one in each vein) for the measurement of arterial pressure and the administration of drugs, respectively. A supra-pubic incision ~1/2 inch lateral to the penis is made to expose the urethers, bladder and urethra. The urethers are ligated and cannulated so that urine flows freely into beakers. The dome of the bladder is retracted to facilitate dissection of the proximal and distal urethra. Umbilical tape is passed beneath the urethra at the bladder neck and another piece of umbilical tape is placed under the distal urethra approximately 1-2 cm distal to the prostate. The bladder is incised and a Millar micro-tip pressure transducer is advanced into the urethra. The bladder incision is sutured with 2-0 or 3-0 silk (purse-string suture) to hold the transducer. The tip of the transducer is placed in the prostatic urethra and the position of the Millar catheter is verified by gently squeezing the prostate and noting the large change in urethral pressure.

Phenylephrine, an alpha-1 adrenergic agonist, is administered (0.1-100 ug/kg, iv; 0.05 ml/kg volume) in order to construct dose response curves for changes in intra-urethral and arterial pressure. Following administration of increasing doses of an alpha adrenergic antagonist (or vehicle), the effects of phenylephrine on arterial pressure and intra-urethral pressure are re-evaluated. Four or five phenylephrine dose-response curves are generated in each animal (one control, three or four doses of antagonist or vehicle). The relative antagonist potency on phenylephrine induced changes in arterial and intra-urethral pressure are determined by Schild analysis. The family of averaged curves are fit simultaneously (using ALLFIT software

package) with a four paramenter logistic equation constraining the slope, minimum response, and maximum response to be constant among curves. The dose ratios for the antagonist doses (rightward shift in the dose-response curves from control) are calculated as the ratio of the ED_{50}'s for the respective curves. These dose-ratios are then used to construct a Schild plot and the Kb (expressed as ug/kg, iv) determined. The Kb (dose of antagonist causing a 2-fold rightward shift of the phenylephrine dose-response curve) is used to compare the relative potency of the antagonists on inhibiting phenylephrine responses for intra-urethral and arterial pressure. The relative selectivity is calculated as the ratio of arterial pressure and intra-urethral pressure Kb's. Effects of the alpha-1 antagonists on baseline arterial pressure are also monitored. Comparison of the relative antagonist potency on changes in arterial pressure and intra-urethral pressure provide insight as to whether the alpha receptor subtype responsible for increasing intra-urethral pressure is also present in the systemic vasculature. According to this method, one is able to confirm the selectivity of alpha1C adrenergic receptor antagonists that prevent the increase in intra-urethral pressure to phenylephrine without any activity at the vasculature.

At the end of the experiment, the dogs are killed via an overdose of intravenously administered pentobarbital or saturated KCl.

EXAMPLE 15

1,1-Dioxido-2-(4-(4-(2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one

Step 1: A mixture of 15.4 g 4-piperidone hydrochloride hydrate, 200 mL ether, 100 mL saturated aqueous Na_2CO_3 solution and 21.8 g di-t-butyldicarbonate was vigorously stirred for 48 h. The layers were separated and the organic layer was washed with two 150 mL portions of 10% aqueous citric acid, dried over $MgSO_4$. Removal of solvents

under reduced pressure gave 18.9 g (95%) N-t-butyloxycarbonyl-4-piperidone as a white solid.

Step 2: A mixture of 6.0 g N-t-butyloxycarbonyl-4-piperidone, 3.3 g of 2-aminophenol, 25 mL of 1,2-dichloroethane, 25 mL of glacial acetic acid, and 500 mg powdered 4Å molecular sieves was stirred under inert atmosphere. After 30 min, 6.4 g sodium triacetoxyborohydride was added stirring was continued for 38 h. The reaction mixture was poured into 400 mL ethyl acetate and 200 mL saturated aqueous $NaHCO_3$ and the layers separated. The organic layer was washed with brine (2 x 100 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Chromatography of the crude product on silica gel, eluting with a gradient of 1-3% methanol/methylene chloride containing 0.5% concentrated NH_4OH gave 6.95 g (79%)1-t-butyloxycarbonyl-4-(2-hydroxyphenylamino)piperidine as an orange foam.

Step 3: To a stirred solution of 6.95 g 1-t-butyloxycarbonyl-4-(2-hydroxyphenylamino)piperidine and 6.2 mL diisopropylethylamine in 120 mL tetrahydrofuran cooled to 0°C was added 3.0 g triphosgene. The reaction was stirred 30 min at 0°C and then at room temperature 2 h. The precipitate was removed by filtration, the filtrate concentrated at reduced pressure and partitioned between 250 mL ethyl acetate and 100 mL saturated aqueous Na_2CO_3. The layers were separated, the organic layer washed with 100 mL of saturated aqueous Na_2CO_3, 100 mL of water, 100 mL of brine , dried over $MgSO_4$, and concentrated under reduced pressure. Chromatography of the crude product on silica gel, eluting with a gradient of 40-50% ethyl acetate-hexanes gave 6.0 g (79%) 1-((1-t-butyloxycarbonyl)piperidin-4-yl)-3-benzoxazolin-2-one as a yellow foam.

Step 4: A stirred solution of 6.0 g (19 mmol) 1-((1-t-butyloxycarbonyl)piperidin-4-yl)-3-benzoxazolin-2-one in 120 mL ethyl acetate was cooled to -78°C and a stream of hydrogen chloride gas was introduced with a fritted dispersion tube for 15 min. The mixture was allowed to warm to 0°C for 1 h, then room temperature for 2 h. The resulting precipitate was collected by filtration. Drying

at reduced pressure for 8 h gave 4.2 g (16.5 mmol, 88%) of the hydrochloride salt of 1-(4-piperidinyl)-3-benzoxazolin-2-one as an off-white solid.

Step 5: A mixture of 430 mg (1.7 mmol) of the hydrochloride salt of 1-(4-piperidinyl)-3-benzoxazolin-2-one and 588 mg (1.9 mmol) of 2-(4-bromobutyl)-1,1-dioxido-1,2-benzothiazol-3(2H)-one, 20 mL dry dimethylformamide and 0.6 mL (3.5 mmol) diisopropylethylamine was warmed to 80°C for 3 h. The solvents were removed under reduced pressure and the crude oily product dissolved in 100 mL ethyl acetate, washed with saturated aqueous $NaHCO_3$ (3 x 30 mL), brine (1 x 30 mL), dried over Na_2SO_4 and concentrated at reduced pressure. Chromatography of the crude product on silica gel, eluting with a gradient of 10% methanol in methylene chloride and recrystallization from ethyl acetate gave 300 mg (40%) of 1,1-dioxido-2-(4-(4-(2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one as an off-white crystalline solid. Analysis calculated for $C_{23}H_{25}N_3O_5S$ C: 60.64, H: 5.53, N: 9.22 found C: 60.04, H: 5.50, N: 9.29. ^{1}H NMR (300 MHz, $CDCl_3$) 8.07 (dd, J = 6.54, 2.2 Hz, 1H), 7.93 (m, 1H), 7.85 (m, 2H), 7.18 (m, 4H), 4.21 (tt, J = 12.4, 4.34 Hz, 1H), 3.85 (t, J = 7.27 Hz, 2H), 3.07 (d, J = 11.67 Hz, 2H), 2.45 (t, J = 7.57 Hz, 2H), 2.35 (dt, J = 12.45, 3.71 Hz, 2H), 2.11 (dt, J = 12.1, 1.84 Hz, 2H), 1.90 (m, 4H), 1.64 (m, 2H).

EXAMPLE 16

1,1-Dioxido-2-(4-(4-(3,4-dihydro-2-oxo-(1*H*)-quinolin-1-yl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one

From the hydrochloride salt of 3,4-dihydro-1-(4-piperidyl)-2(1*H*)-quinolinone prepared according to H. Ogawa et. al. *J. Med. Chem.* **1993**, *36*, 2011-2017, and 2-(4-bromobutyl)-1,1-dioxido-1,2-benzothiazol-3(2H)-one using the procedure described for Example 15, Step 5 there was obtained 1,1-dioxido-2-(4-(4-(3,4-dihydro-2-oxo-(1H)-quinolin-1-yl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one

as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) 8.07 (dd, J = 6.5, 2.3 Hz, 1H), 7.92 (t, J = 6.73 Hz, 1H), 7.84 (m, 2H), 7.21 (t, J = 8.73 Hz, 2H), 7.19 (m, 1H), 6.99 (t, J = 7.13 Hz, 1H), 4.35 (tt, J = 12.2, 4.2 Hz, 1H), 3.83 (t, J = 7.32 Hz, 2H), 3.04 (d, J = 11.42 Hz, 2H), 2.81 (t, J = 6.59 Hz, 2H), 2.61 (m, 3H), 2.43 (t, J = 7.19 Hz, 2H), 2.09 (t, J = 11.71 Hz, 2H), 1.88 (m, 2H), 1.69 (m, 5H).

EXAMPLE 17

1,1-Dioxido-2-(4-(4-(1,2-dihydro-4(H)-2-oxo-3,1-benzoxazinyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one

Step1: A mixture of 20 g of N-t-butyloxycarbonyl-4-piperidinone, 13 g of 2-aminobenzyl alcohol 14 mL of acetic acid and 500 mL of toluene was refluxed under inert atmosphere with azeotropic removal of water for 16 h. After cooling to ambient temperature, 14 g of sodium cyanoborohydride and 200 mL tetrahydrofuran were added and the mixture was stirred at ambient temperature for 24 h. The reaction mixture was concentrated under reduced pressure, the residue was dissolved in 750 mL of ethyl acetate and washed with saturated aqueous $NaHCO_3$ (4x 500 mL) and brine (250 mL). The organic layer was dried over $MgSO_4$, and the solvent was removed under reduced pressure. Chromatography of the crude product on silica gel, eluting with a gradient of 15-30% ethyl acetate-hexanes gave 24 g (78%) of 1-t-butyloxycarbonyl-4-((2-hydroxymethyl)phenylamino)piperidine as a gum .

Step 2. To a stirred mixture of 24 g of 1-t-butyloxycarbonyl-4-((2-hydroxymethyl)-phenylamino)piperidine, 250 mL of tetrahydrofuran, 41 mL of diisopropylethylamine cooled to 0°C was added 8.54 g of triphosgene. The reaction was stirred at 0°C for 1h, and then at ambient temperature for 72 h. Ether (250 mL) was added, the mixture was cooled to 0°C for 3 h, the precipitate removed by filtration and the filtrate was concentrated under reduced pressure. The residue was dissolved in 750 mL of ethyl acetate, washed with 5% aqueous citric

acid (2x 500 mL), water (250 mL), saturated aqueous $NaHCO_3$ (2x 500 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was boiled in ether (ca. 200 mL) until the solid had dissolved. Cooling overnight gave 19 g of 1-((1-t-butyloxycarbonyl)piperidin-4-yl)-1,2-dihydro-4(H)-3,1-benzoxazin-2-one as off-white crystals (75% yield).

Step 4. A stream of hydrogen chloride gas was dispersed through a stirred, ice cold solution of 19 g of 1-((1-t-butyloxycarbonyl)-piperidin-4-yl)-1,2-dihydro-4(H)-3,1-benzoxazin-2-one in 500 mL of ethyl acetate for 30 min. Stirring was continued at 0°C for 1 h, then at ambient temperature for 1 h. The suspension was diluted with 250 mL of ether, aged for 1 h at 0°C, and the solid product was collected by filtration. Drying under reduced pressure for 18 h, gave 14 g of the hydrochloride salt of 1-(4-piperidinyl)-1,2-dihydro-4(H)-3,1-benzoxazin-2-one as an off-white solid (91%)

Step 5: From the hydrochloride salt of 1-(4-piperidinyl)-1,2-dihydro-4(H)-3,1-benzoxazin-2-one, and 2-(4-bromobutyl)-1,1-dioxido-1,2-benzothiazol-3(2H)-one using the procedure described for Example 15, Step 5 there was obtained a white solid, HCl salt: ^{1}H NMR (400 MHz, CD_3OD) 8.10 (t, J = 7.33 Hz, 1H), 7.99 (m, 3H), 7.42 (t, J = 7.14 Hz, 1H), 7.27 (t, J = 7.51 Hz, 2H), 7.16 (t, J = 7.69 Hz, 1H), 5.17 (s, 2H), 4.27 (t, J = 12.08 Hz, 1H), 3.87 (t, J = 6.22 ppm, 2H), 3.67 (m, 3H), 3.19 (m, 3H), 2.98 (m, 2H), 2.16 (d, J = 12.5 Hz, 2H), 1.92 (m, 4H).

EXAMPLE 18

1,1-Dioxido-2-(4-(4-(2-oxo-(1H)-quinolin-1-yl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one

From the hydrochloride salt of 1-(4-piperidyl)-2(1*H*)-quinolinone was prepared according to H. Ogawa et. al. *J. Med. Chem.* **1993**, *36*, 2011-2017, and 2-(4-bromobutyl)-1,1-dioxido-1,2-benzothiazol-

3(2H)-one using the procedure described for Example 15, Step 5 there was obtained a white solid:^{1}H NMR (300 MHz, $CDCl_3$) 8.08 (d, J = 6.73 Hz, 1H), 7.90 (m, 3H), 7.7 (d, J = 9.5 Hz, 1H), 7.6 (d, J = 9.2 Hz, 1H), 7.56 (d, J = 7.62 Hz, 1H), 7.26 (m, 2H), 6.71 (d, J = 9.47 Hz, 1H), 3.85 (br m, 3H), 3.45 (br m, 1H), 3.25 (br m, 3H), 3.14 (br m, 6H), 1.95 (br s, 4H).

EXAMPLE 19

1,1-Dioxido-2-(4-(4-(2-oxo-(1H)-quinolin-1-yl)-piperidin-1-yl)-butyl)-5-nitro-1,2-benzisothiazol-3(2H)-one

From the hydrochloride salt of 1-(4-piperidyl)-2(1*H*)-quinolinone prepared according to H. Ogawa et. al. *J. Med. Chem.* **1993**, *36*, 2011-2017, and 2-(4-bromobutyl)-5-nitro-1,1-dioxido-1,2-benzothiazol-3(2H)-one using the procedure described for Example 15, Step 5 there was obtained a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) 8.88 (d, J = 1.9 Hz, 1H), 8.73 (dd, J = 8.36, 1.71 Hz, 1H), 8.15 (d, J = 8.36 Hz, 1H), 7.79 (br m, 1H), 7.62 (d, J = 3.47 Hz, 1H), 7.51 (m, 2H), 7.20 (m, 2H), 6.66 (d, J = 9.33 Hz, 1H), 3.91 (t, J = 7.33 Hz, 2H), 2.85 (br m, 2H), 2.48 (t, J = 8.27 Hz, 2H), 2.21 (t, J = 10.65 Hz, 2H).

EXAMPLE 20

6-Chloro-1,1-dioxido-2-(4-(4-(2-oxo-(1H)-quinolin-1-yl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one

From the hydrochloride salt of 1-(4-piperidyl)-2(1*H*)-quinolinone prepared according to H. Ogawa et. al. *J. Med. Chem.* **1993**, *36*, 2011-2017, and 2-(4-bromobutyl)-6-chloro-1,1-dioxido-1,2-benzothiazol-3(2H)-one using the procedure described for Example 15, Step 5 there was obtained a white solid, HCl salt: ^{1}H NMR (300MHz, CD_3OD) 8.25 (d, J = 1.66 Hz, 1H), 8.08 (d, J = 8.17 Hz, 1H), 7.98 (dd, J = 8.24, 1.71 Hz, 1H), 7.89 (d, J = 9.52 Hz, 1H), 7.85 (d, J = 8.55 Hz, 1H), 7.71 (d, J = 7.68 Hz, 1H), 7.68 (t, J = 7.57 Hz,

1H), 7.33 (t, J = 7.65 Hz, 1H), 6.59 (d, J = 9.52 Hz, 1H), 5.06 (br m, 1H), 3.88 (t, J = 6.3 Hz, 2H), 3.69 (d, J = 9.87 Hz, 2H), 3.26 (m, 6H), 1.94 (m, 6H).

EXAMPLE 21

5-Chloro-1,1-dioxido-2-(4-(4-(2-oxo-(1H)-quinolin-1-yl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one

From the hydrochloride salt of 1-(4-piperidinyl)-3-benzoxazolin-2-one and 2-(4-bromobutyl)-6-chloro-1,1-dioxido-1,2-benzothiazol-3(2H)-one using the procedure described for Example 15, Step 5 there was obtained a white solid, HCl salt: ^{1}H NMR (300 MHz, CD_3OD) 8.11 (d, J = 7.81 Hz, 1H), 8.13 (s, 1H), 8.02 (dd, J = 8.3, 1.7 Hz, 1H), 7.90 (d, J = 9.52 Hz, 1H), 7.85 (d, J = 8.85 Hz, 1H), 7.71 (d, J = 7.57 Hz, 1H), 7.67 (t, J = 8.97 Hz, 1H), 7.33 (t, J = 7.32 Hz, 1H), 6.59 (d, J = 9.47 Hz, 1H), 5.08 (br m, 1H), 3.89 (t, J = 6.11 Hz, 2H), 3.71 (d, J = 8.74 Hz, 2H), 3.30 (br m, 6H), 2.0-1.9 (m, 6H).

EXAMPLE 22

1,1-Dioxido-2-(4-(4-(2-oxo-(1H)-quinolin-1-yl)-piperidin-1-yl)-butyl)-7-nitro-1,2-benzisothiazol-3(2H)-one

From the hydrochloride salt of 1-(4-piperidinyl)-3-benzoxazolin-2-one and 2-(4-bromobutyl)-6-nitro-1,1-dioxido-1,2-benzothiazol-3(2H)-one using the procedure described for Example 15, Step 5 there was obtained a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) 8.65 (d, J = 8.19 Hz, 1H), 8.44 (d, J = 7.63 Hz, 1H), 8.10 (t, J = 8.11 Hz, 1H), 7.81 (br s, 1H), 7.61 (d, J = 9.34 Hz, 1H), 7.52 (m, 2H), 7.19 (t, J = 7.33 Hz, 1H), 6.67 (d, J = 9.28 Hz, 1H), 3.95 (t, J = 7.38 Hz, 2H), 3.10 (d, J = 10.37 Hz, 2H), 2.86 (br s, 2H), 2.49 (t, J = 6.95 Hz, 2H), 2.22 (t, J = 10.74 Hz, 2H), 1.98 (m, 2H), 1.70 (br m, 5H).

EXAMPLE 23

1,1-Dioxido-2-(4-(4-(2-oxo-(1H)-quinolin-1-yl)-piperidin-1-yl)-butyl)-4-methoxy-1,2-benzisothiazol-3(2H)-one

From the hydrochloride salt of 1-(4-piperidyl)-2(1*H*)-quinolinone prepared according to H. Ogawa et. al. *J. Med. Chem.* **1993**, *36*, 2011-2017, and 2-(4-bromobutyl)-4-methoxy-1,1-dioxido-1,2-benzothiazol-3(2H)-one using the procedure described for Example 15, Step 5 there was obtained a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) 7.80 (t, J = 8.1 Hz, 2H), 7.60 (d, J = 9.33 Hz, 2H), 7.51 (m, 2H), 7.25 (m, 3H), 6.66 (d, J = 9.27 Hz, 1H), 4.06 (s, 2H), 3.80 (t, J = 6.9 Hz, 2H), 3.09 (dd, J = 9.8, 1.8 Hz, 2H), 2.84 (m, 2H), 2.46 (t, J = 7.2 Hz, 2H), 2.19 (t, J = 11.6 Hz, 2H), 1.89 (br m, 2H), 1.69 (br m, 3H), 1.58 (s, 3H).

EXAMPLE 24

1,1-Dioxido-2-(4-(4-(2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-5-nitro-1,2-benzisothiazol-3(2H)-one

From the hydrochloride salt of 1-(4-piperidinyl)-3-benzoxazolin-2-one and 2-(4-bromobutyl)-5-nitro-1,1-dioxido-1,2-benzothiazol-3(2H)-one using the procedure described for Example 15, Step 5 there was obtained a white solid, HCl salt: ^{1}H NMR (300 MHz, CD_3OD) 8.82 (m, 2H), 8.39 (d, J = 8.98 Hz, 1H), 7.25 (m, 4H), 4.50 (tt, J = 8.01, 3.96 Hz, 1H), 3.93 (t, J = 6.05 Hz, 2H), 3.74 (d, J = 12.94 Hz, 2H), 3.26 (m, 4H), 2.73 (m, 2H), 2.17 (d, J = 13.9 Hz, 2H), 1.93 (br m, 4H).

EXAMPLE 25

6-Chloro-1,1-dioxido-2-(4-(4-(2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one

From the hydrochloride salt of 1-(4-piperidinyl)-3-benzoxazolin-2-one and 2-(4-bromobutyl)-6-chloro-1,1-dioxido-1,2-benzothiazol-3(2H)-one using the procedure described for Example 15, Step 5 there was obtained a white solid, HCl salt: ^{1}H NMR (300 MHz, CD_3OD) 8.22 (d, J = 1.41 Hz, 1H), 8.07 (dd, J = 8.3, 2.63 Hz, 1H), 7.96 (dd, J = 8.19, 1.65 Hz), 7.33 (d, J = 7.13 Hz, 1H), 7.23 (m, 2H), 4.49 (tt, J = 12.21, 4.21 Hz, 1H), 3.88 (t, J = 5.86 Hz, 2H), 3.74 (d, J = 11.72 Hz, 2H), 3.23 (br m, 4H), 2.73 (m, 2H), 2.17 (d, J = 13.43 Hz, 2H), 1.9 (br m, 4H).

EXAMPLE 26

5-Chloro-1,1-dioxido-2-(4-(4-(2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one

From the hydrochloride salt of 1-(4-piperidinyl)-3-benzoxazolin-2-one and 2-(4-bromobutyl)-5-chloro-1,1-dioxido-1,2-benzothiazol-3(2H)-one using the procedure described for Example 15, Step 5 there was obtained a white solid, HCl salt: ^{1}H NMR (300 MHz, CD_3OD) 8.10 (d, J = 6.59 Hz, 1H), 8.11 (s, 1H), 7.29 (m, 2H), 7.21 (m, 2H), 4.49 (tt, J = 12.21, 4.21 Hz, 1H), 3.88 (t, J = 5.86 Hz, 2H), 3.74 (d, J = 11.72 Hz, 2H), 3.23 (br m, 4H), 2.73 (m, 2H), 2.17 (br d, 2H), 1.9 (br m, 4H).

EXAMPLE 27

1,1-Dioxido-2-(4-(4-(2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-7-nitro-1,2-benzisothiazol-3(2H)-one

From the hydrochloride salt of 1-(4-piperidinyl)-3-benzoxazolin-2-one and 2-(4-bromobutyl)-7-nitro-1,1-dioxido-1,2-benzothiazol-

3(2H)-one using the procedure described for Example 15, Step 5 there was obtained a white solid, HCl salt: ^{1}H NMR (300 MHz, CD_3OD) 8.76 (d, J = 8.25 Hz, 1H), 8.50 (d, J = 7.76 Hz, 1H), 8.22 (t, J = 7.76 Hz), 7.24 (m, 4H), 4.49 (tt, J = 12.21, 4.21 Hz, 1H), 3.96 (t, J = 6.01 Hz, 2H), 3.76 (d, J = 11.7 Hz, 2H), 3.23 (m, 4H), 2.73 (m, 2H), 2.17 (dd, J = 14.5, 2.2 Hz, 2H), 1.9 (m, 4H).

EXAMPLE 28

1,1-Dioxido-2-(4-(4-(2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-4-methoxy-1,2-benzisothiazol-3(2H)-one

From the hydrochloride salt of 1-(4-piperidinyl)-3-benzoxazolin-2-one and 2-(4-bromobutyl)-4-methoxy-1,1-dioxido-1,2-benzothiazol-3(2H)-one using the procedure described for Example 15, Step 5 there was obtained a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) 7.83 (t, J = 8.06 Hz, 1H), 7.49 (d, J = 7.69 Hz, 1H), 7.46 (d, J = 7.51 Hz, 1H), 7.30 (d, J = 8.6 Hz, 1H), 7.17 (m, 3H), 4.56 (dt, J = 11.72, 4.21 Hz, 1H), 4.07 (s, 3H) 3.79 (m, 4H), 3.16 (m, 2H), 2.88 (m, 4H), 2.07 (d, J = 13.0 Hz, 2H), 1.96 (m, 4H).

EXAMPLE 29

1,1-Dioxido-2-(4-(4-(5-chloro-2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one

From the hydrochloride salt of 5-chloro-1-(4-piperidinyl)-3-benzoxazolin-2-one and 2-(4-bromobutyl)-1,1-dioxido-1,2-benzothiazol-3(2H)-one using the procedure described for Example 15, Step 5 there was obtained a white solid, HCl salt: ^{1}H NMR (400 MHz, CD_3OD) 8.10 (td, J = 6.0, 1.2 Hz, 2H), 8.02-7.94 (overlapping dt, 2H), 7.43 (d, J = 1.8 Hz, 1H), 7.24 (d, J = 8.4 Hz, 1H), 7.16 (dd, J = 8.6, 2.0 Hz, 1H), 4.43 (tt, J = 12.4, 4.4, 1H), 3.88 (t, J = 6.4, 2H), 3.66 (d, J = 11.5, 2H), 3.16-3.05 (m, 4H), 2.66 (qd, J = 13.0, 3.7, 2H), 2.13 (d, J = 13.4, 2H), 2.01-1.88 (m, 4H).

EXAMPLE 30

1,1-Dioxido-2-(4-(4-(3a-(*R*)-8a-(*S*)-2-oxo-3,3a,8,8a-tetrahydro-2H-indeno[1,2-d]oxazolinyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one

From the hydrochloride salt of 4-(3a-(R)-8a-(S)-2-oxo-3,3a,8,8a-tetrahydro-2H-indeno[1,2-d]oxazolinyl)-piperidine and 2-(4-bromobutyl)-1,1-dioxido-1,2-benzothiazol-3(2H)-one using the procedure described for Example 15, Step 5 there was obtained a white solid, HCl salt: ^{1}H NMR (400 MHz, CD_3OD) 8.10-8.07 (m, 1H), 8.02-7.94 (m, 2H), 7.59 (d, J = 7.1 Hz, 1H), 7.32-7.31 (m, 4H), 5.37-5.30 (m, 2H), 3.86 (m, 3H), 3.55-3.41 (m, 4H), 3.25-2.98 (m, 5H), 2.55 (m, 2H), 2.14 (m, 1H), 1.94-1.77 (m, 4H),

EXAMPLE 31

1,1-Dioxido-2-(4-(4-(2-oxonaphth[2,3-d]oxazolinyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one

From the hydrochloride salt of 4-(2-oxonaphth[2,3-d]oxazolinyl)-piperidine and 2-(4-bromobutyl)-1,1-dioxido-1,2-benzothiazol-3(2H)-one using the procedure described for Example 15, Step 5 there was obtained a white solid, HCl salt: ^{1}H NMR (400 MHz, CD_3OD) 8.11 (td, J = 6.5, 0.9 Hz, 2H), 8.02-7.94 (m, 2H), 7.89 (d, J = 8.2 Hz, 2H), 7.68 (d, J = 5.3 Hz, 2H), 7.50-7.42 (m, 2H), 4.58 (tt, J = 12.3, 4.0 Hz, 1H), 3.90 (t, J = 6.4 Hz, 2H), 3.72 (d, J = 13.0 Hz, 2H), 3.22-3.15 (m, 4H), 2.80 (qd, J = 12.8, 3.0 Hz, 2H), 2.21 (d, J = 13.7 Hz, 2H), 2.00-1.92 (m, 4H).

EXAMPLE 32

1,1-Dioxido-2-(4-(4-(6-methyl-2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one

From the hydrochloride salt of 4-(6-methyl-2-oxo-3-benzoxazolinyl)-piperidine and 2-(4-bromobutyl)-1,1-dioxido-1,2-benzothiazol-3(2H)-one using the procedure described for Example 15, Step 5 there was obtained a white solid, HCl salt: ^{1}H NMR (400 MHz, CD3OD) 8.09 (td, J = 5.7, 1.5 Hz, 2H), 8.03-7.94 (m, 2H), 7.21 (d, J = 8.1 Hz, 1H), 7.11 (s, 1H), 7.06 (d, J = 8.0 Hz, 1H), 4.46 (tt, J = 12.2, 4.0 Hz, 1H), 3.88 (t, J = 6.4 Hz, 2H), 3.71 (d, J = 12.5 Hz, 2H), 3.26-3.16 (m, 4H), 2.71 (qd, J = 13.5, 3.5 Hz, 2H), 2.38 (s, 3H), 2.14 (d, J = 14.1 Hz, 2H), 1.97-1.91 (m, 4H).

EXAMPLE 33

1,1-Dioxido-2-(4-(4-(2-oxo-5-phenyl-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one

From the hydrochloride salt of 4-(2-oxo-5-phenyl-3-benzoxazolinyl)-piperidine and 2-(4-bromobutyl)-1,1-dioxido-1,2-benzothiazol-3(2H)-one using the procedure described for Example 15, Step 5 there was obtained a white solid, HCl salt: ^{1}H NMR (400 MHz, CD3OD) 8.11-8.07 (overlapping t, 2H), 8.02-7.94 (m, 2H), 7.64 (d, J = 7.1 Hz, 2H), 7.58 (d, J = 1.5 Hz, 1H), 7.47-7.41 (m, 3H), 7.38-7.33 (m, 2H), 4.57 (tt J = 12.4, 4.2 Hz, 1H), 3.88 (t, J = 6.4 Hz, 2H), 3.71 (d, J = 12.1 Hz, 2H), 3.23-3.13 (m, 4H), 2.77 (qd, J = 14.0, 3.0 Hz, 2H), 2.18 (d, J = 13.9, 2H), 1.97-1.90 (m, 4H).

EXAMPLE 34

1,1-Dioxido-2-(4-(4-(6-methoxy-2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one

From the hydrochloride salt of 4-(6-methoxy-2-oxo-3-benzoxazolinyl)-piperidine and 2-(4-bromobutyl)-1,1-dioxido-1,2-benzothiazol-3(2H)-one using the procedure described for Example 15, Step 5 there was obtained a white solid, HCl salt: ^{1}H NMR (400 MHz, CD_3OD) 8.14 (td, J = 6.4, 1.4 Hz, 2H), 8.05-8.00 (overlapping td, 2H), 7.26 (d, J = 8.6 Hz, 1H), 6.99 (d, J = 2.4 Hz, 1H), 6.86 (dd, J = 8.8, 2.4 Hz, 1H), 4.48 (tt, J = 12.1, 4.2 Hz, 1H), 3.92 (t, J = 6.2 Hz, 2H), 3.83 (s, 3H), 3.75 (d, J = 12.1, 2H), 3.34-3.22 (m, 4H), 2.74 (qd, J = 12.6, 3.6 Hz, 2H), 2.19 (d, J = 13.5 Hz, 2H), 2.00-1.95 (m, 4H).

EXAMPLE 35

1,1-Dioxido-2-(4-(4-(6-carbomethoxy-2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one

From the hydrochloride salt of 4-(6-carbomethoxy-2-oxo-3-benzoxazolinyl)-piperidine and 2-(4-bromobutyl)-1,1-dioxido-1,2-benzothiazol-3(2H)-one using the procedure described for Example 15, Step 5 there was obtained a white solid, HCl salt: ^{1}H NMR (400 MHz, CD_3OD) 8.01 (t, J = 6.8 Hz, 2H), 7.94-7.86 (m, 3H), 7.78 (d, J = 1.5 Hz, 1H), 7.31 (d, J = 8.4, 1H), 4.40 (m, 1H), 3.83 (s, 3H), 3.79 (t, J = 6.6, 2H), 3.72 (d, J = 7.1, 2H), 3..05 (m, 2H), 2.97 (m, 2H), 2.60 (m, 2H), 2.05 (d, J = 12.5, 2H), 1.89-1.79 (m, 4H).

EXAMPLE 36

1,1-Dioxido-2-(4-(4-(5-ethylsulfonyl-2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one

From the hydrochloride salt of 4-(5-ethylsulfonyl-2-oxo-3-benzoxazolinyl)-piperidine and 2-(4-bromobutyl)-1,1-dioxido-1,2-benzothiazol-3(2H)-one using the procedure described for Example 15, Step 5 there was obtained a white solid, HCl salt: ^{1}H NMR (400 MHz, CD3OD) 8.01 (t, J = 6.0 Hz, 2H), 7.93-7.87 (m, 2H), 7.77 (s, 1H), 7.67 (d, J = 7.1 Hz, 1H), 7.42 (d, J = 8.2 Hz, 1H), 4.48 (m, 1H), 3.79 (m, 2H), 3.60 (d, J = 11.2 Hz, 2H), 3.14-3.06 (overlapping q & m, 6H), 2.61 (br q, J = 12.5 Hz, 2H), 2.10 (d, J = 13.4 Hz, 2H), 1.85 (m, 4H), 1.15 (t, J = 6.2 Hz, 3H),

EXAMPLE 37

1,1-Dioxido-2-(4-(4-(2-oxo-3-oxazolo[4,5-b]pyridyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one

From the hydrochloride salt of 4-(2-oxo-3-oxazolo[4,5-b]pyridyl)-piperidine and 2-(4-bromobutyl)-1,1-dioxido-1,2-benzothiazol-3(2H)-one using the procedure described for Example 15, Step 5 there was obtained a white solid, HCl salt: ^{1}H NMR (400 MHz, CD3OD) 8.03-7.99 (m, 3H), 7.94-7.85 (2 overlapping td, 2H), 7.49 (dd, J = 8.0, 1.2 Hz, 1H), 7.07 (dd, J = 8.0, 5.0 Hz, 1H), 4.56 (tt, J = 12.1, 4.1 Hz, 1H), 3.79 (t, J = 6.4 Hz, 2H), 3.63 (t, J = 12.8 Hz, 2H), 3.20-3.09 (m, 4H), 2.82 (qd, J = 13.3, 3.5 Hz, 2H), 2.09 (d, J = 13.4, 2H), 1.88-1.78 (m, 4H).

EXAMPLE 38

1,1-Dioxido-2-(4-(4-(7-carbethoxy-2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one

From the hydrochloride salt of 4-(7-carbethoxy-2-oxo-3-benzoxazolinyl)-piperidine and 2-(4-bromobutyl)-1,1-dioxido-1,2-benzothiazol-3(2H)-one using the procedure described for Example 15, Step 5 there was obtained a white solid, HCl salt: ^{1}H NMR (400 MHz, CD_3OD) 8.01 (td, J = 6.4, 1.5 Hz, 2H), 7.94-7.86 (m, 2H), 7.63 (dd, J = 8.1, 1.1 Hz, 1H), 7.47 (dd, J = 7.9, 1.1 Hz, 1H), 7.26 (t, J = 8.1 Hz, 1H), 4.42 (tt, J = 12.1, 4.0 Hz, 1H), 3.87 (s, 3H), 3.80 (t, J = 6.2, 2H), 3.63 (d, J = 12.8 Hz, 2H), 3.16-3.06 (m, 4H), 2.65 (qd, J = 13.0, 4.0 Hz, 2H), 2.09 (d, J = 13.5 Hz, 2H), 1.89-1.83 (m, 4H).

EXAMPLE 39

1,1-Dioxido-2-(4-(4-(5-*tert*-butyl-2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one

From the hydrochloride salt of 4-(5-tert-butyl-2-oxo-3-benzoxazolinyl)-piperidine and 2-(4-bromobutyl)-1,1-dioxido-1,2-benzothiazol-3(2H)-one using the procedure described for Example 15, Step 5 there was obtained a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) 8.07 (dd, J = 6.6, 2.25 Hz, 1H), 7.88 (m, 3H), 7.19 (s, 1H), 7.11 (s, 2H), 4.17 (tt, J = 12.21, 3.66 Hz, 1H), 3.85 (t, J = 7.14 Hz, 2H), 3.09 (d, J = 10.85 Hz, 2H), 2.46 (t, J = 7.38 Hz, 2H), 2.36 (dt, J = 12.15, 3.5 Hz, 2H), 2.13 (dt, J = 10.89, 1.27 Hz, 2H), 1.91 (m, 4H), 1.66 (m, 2H), 1.342 (s, 9H).

EXAMPLE 40

1,1-Dioxido-2-(4-(4-(5,7-dimethyl-2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one

From the hydrochloride salt of 4-(5,7-dimethyl-2-oxo-3-benzoxazolinyl)-piperidine and 2-(4-bromobutyl)-1,1-dioxido-1,2-benzothiazol-3(2H)-one using the procedure described for Example 15, Step 5 there was obtained a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) 8.08 (d, J = 7.27 Hz, 1H), 7.90 (m, 3H), 7.65 (br m, 1H), 6.752 (s, 1H), 4.55 (br m, 1H), 3.85 (br t, 2H), 3.70 (br m, 2H), 3.32 (br m, 2H), 3.10 (br m, 2H), 2.87 (br m, 2H), 2.413 (s, 3H), 2.318 (s, 3H), 2.06 (br m, 6H).

EXAMPLE 41

2-(4-Bromobutyl)-1,1-dioxido-1,2-benzothiazol-3(2H)-one

The general procedure of J. D. Commerford and H. B. Donahue *J. Org. Chem.* **1956**, *21*, 583-4 was modified: A mixture of 6 g of sodium saccharin, 100 mL of 1,4-dibromobutane, and 5 mL of N,N-dimethylformamide was heated at 50°C overnight. After cooling to ambient temperature, the mixture was diluted with 250 mL of ether and 50 mL of water. The aqueous layer was extracted with two additional 50 mL portions of ether and the combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The excess 1,4-dibromobutane was removed by short path vacuum distillation and the oily residue purified by crystallization from ether-hexane, mp 71-2°C.

EXAMPLE 42

2-(4-Bromobutyl)-1,1-dioxido-5-methoxy-1,2-benzothiazol-3(2H)-one

The general procedure of J. D. Commerford and H. B. Donahue *J. Org. Chem.* **1956**, *21*, 583-4 was modified: A mixture of 0.5 g of

3,3-dioxido-5-methoxy-1,2-benzothiazol-3(2H)-one prepared as described by J. G. Lombardino, *J. Org. Chem.* **1971**, *36*, 1843-5, 1 mL of N,N-dimethylformamide and 0.1 g of sodium hydride 60% oil dispersion was stirred at ambient temperature for 15 min, and 1.4 mL of 1,4-dibromobutane was added. After stirring at ambient temperature overnight, the mixture was diluted with 25 mL of ethyl acetate, washed with 25 mL of sat'd $NaHCO_3$, 25 mL of sat'd brine and dried over $MgSO_4$. Removal of solvents under reduced pressure and vacuum distillation gave 0.8 g of crude product as a viscous oil which was free of 1,4-dibromobutane by ^{1}H-NMR and was used without further purification.

EXAMPLE 43

2-(4-Bromobutyl)-1,1-dioxido-5-nitro-1,2-benzothiazol-3(2H)-one

The general procedure of J. D. Commerford and H. B. Donahue *J. Org. Chem.* **1956**, *21*, 583-4 was modified: A stirred mixture of 1.0 g of 3,3-dioxido-5-nitro-1,2-benzothiazol-3(2H)-one prepared as described by W. S. Saari and J. E. Schwering, *J. Heterocyclic Chem.* **1986**, *23*, 1253, and 6 mL of 1N NaOH was warmed to dissolution and allowed to cool to ambient temperature for 15 min. The mixture was concentrated to dryness under reduced pressure and the white solid azeotropically dried with 20 mL of toluene. The resulting sodium salt was dissolved in 3 mL of N,N-dimethylformamide and 2.6 mL of 1,4-dibromobutane was added. After stirring at ambient temperature overnight, the mixture was diluted with 25 mL of ethyl acetate, washed with 25 mL of sat'd $NaHCO_3$, 25 mL of sat'd brine and dried over $MgSO_4$. Removal of solvents under reduced pressure and vacuum distillation gave 1.1 g of crude product as a solid which was free of 1,4-dibromobutane by ^{1}H-NMR and was used without further purification: ^{1}H NMR (300 MHz, CDCl3): 8.87 (d, J = 0.5 Hz, 1H), 8.74 (dd, J = 8.38, 2.03 Hz, 1H), 8.15 (dd, J = 8.41, 2.0 Hz, 1H), 3.88 (t, J = 6.8 Hz, 2H), 3.47 (t, J = 6.3 Hz, 2H), 2.02 (m, 4H).

EXAMPLE 44

1,1-Dioxido-2-(4-(spiro-1,3-dihydro-1-oxo-2H-indenyl)-2,4'-piperidin-1'-yl)butyl)-1,2-benzisothiazol-3(2H)-one

Step 1: To a ice cold, stirred mixture of 55 g of ethyl isonipecotate, 200 mL of ether, 200 mL of saturated sodium carbonate and 200 mL of water was added dropwise 40 mL of benzoyl chloride. The resulting mixture was allowed to warm and stir overnight, diluted with 200 mL of ethyl acetate and separated. The organic layer was washed with 200 mL of 1N hydrochloric acid, dried over $MgSO_4$, and concentrated. Drying the residue under vacuum gave 83.3 g (92%) of ethyl 1-benzoyl-4-piperidinecarboxylate as a white solid.

Step 2: A stirred solution of 176 mL of commercial 1M lithium bistrimethylsilylamide in tetrahydrofuran was diluted with 100 mL of tetrahydrofuran and cooled to -78°C under inert atmosphere. A solution of 44 g of ethyl 1-benzoyl-4-piperidinecarboxylate in 200 mL of tetrahydrofuran was added dropwise keeping the temperature below -60°C, followed by 21 mL of benzyl bromide. The resulting mixture was allowed to warm and stir overnight, diluted with 200 mL of 1N hydrochloric acid, 200 mL of ethyl acetate and separated. The organic layer was washed with 200 mL of 1N hydrochloric acid, dried over $MgSO_4$, and concentrated. The residue was dissolved in 300 mL of toluene, filtered and concentrated under reduced pressure. Drying under reduced pressure gave 56.3 g of ethyl 1-benzoyl-4-(phenylmethyl)-4-piperidinecarboxylate as a viscous oil homogeneous by thin layer chromatography, eluting with 1:1 ethyl acetate: hexane, ^1H NMR (300 MHz, $CDCl_3$) 1.20 (t, 3H), 1.40 (m, 1H), 1.60 (m, 1H), 2.07 (m, 1H), 2.22 (m, 1H), 2.85 (d, 2H), 3.08 (m, 1H), 3.65 (m, 1H), 4.12 (q, 2H), 4.65 (m, 1H), 7.04 (m, 2H), 7.24 (m, 3H), 7.38 (m, 5H).

Step 2: A mixture of 65 g of ethyl 1-benzoyl-4-(phenylmethyl)-4-piperidinecarboxylate, 300 g of polyphosphoric acid and 500 mL of xylene was heated at reflux overnight. The xylene layer was decanted off and the residue washed with two additional 100 mL portions of xylene. The residue was dissolved in 1L of water and 1L of ethyl

acetate and separated. The aqueous was extracted with two additional 200 mL portions of ethyl acetate and the combined organic extracts were washed with 500 mL of sat'd Na_2CO_3, water and dried over $MgSO_4$. Removal of solvents under reduced pressure gave 27 g of 1'-benzoyl-1,3-dihydro-1-oxo-spiro(2H-indenyl-2,4'-piperidine) as crystalline solid, mp 149-154°C; ^{1}H NMR (300 MHz, $CDCl_3$) 1.50 (m, 2H), 2.00 (m, 2H), 3.12 (m, 2H), 3.25 (ddd, 2H), 3.90 (m, 1H), 4.62 (m, 1H), 7.43 (m, 1H), 7.63 (dd, 1H), 7.79 (d, 1H).

Step 3: A mixture of 27 g of 1'-benzoyl-1,3-dihydro-1-oxo-spiro(2H-indenyl-2,4'-piperidine) 400 mL of ethanol and 100 mL of conc. hydrochloric acid was heated at reflux for 48 hrs. The mixture was concentrated to remove ethanol, diluted 200 mL with water and extracted with two additional portions of ethyl acetate. The aqueous layer was basified with 20% NaOH and extracted with three 200 mL portions of ethyl acetate. The combined organic extracts were washed with 50 mL of water and dried over $MgSO_4$. Removal of solvents under reduced pressure gave 18 g of 1,3-dihydro-1-oxo-spiro(2H-indene-2,4'-piperidine) as brown solid product: ^{1}H NMR (300 MHz, $CDCl_3$) 1.35 (dd, 2H), 1.62 (br s, 1H), 1.88 (ddd, 2H), 2.81 (ddd, 2H), 3.10 (s, 2H), 3.17 (m, 2H), 7.38 (t, 1H), 7.46 (d, 1H), 7.60 (t, 1H), 7.77 (d, 1H).

Step 4: From 1,3-dihydro-1-oxo-spiro(2H-indenyl-2,4'-piperidine), and 2-(4-bromobutyl)-1,1-dioxido-1,2-benzothiazol-3(2H)-one using the procedure described for Example 15, Step 5 there was obtained 1,1-dioxido-2-(4-(spiro(1,3-dihydro-1-oxo-2H-indene-2,4'-piperidin-1'-yl)butyl)-1,2-benzisothiazol-3(2H)-one as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$): 8.06 (d, J=6.8 Hz, 1H), 7.92 (d, J=6.6 Hz, 1H), 7.89-7.83 (m, 2H), 7.75 (d, J=7.7 Hz, 1H), 7.59 (t, J=7.4 Hz, 1H), 7.44 (d, J=6.96 Hz, 1H), 7.37 (t, J=7.4 Hz, 1H), 3.83 (t, J=7.4 Hz, 2H), 3.02 (s, 2H), 2.95 (t, J=11.36 Hz, 2H), 2.45 (t, J=7.4 Hz, 2H), 2.17-2.01 (m, 4H), 1.94-1.90 (m, 2H), 1.67-1.64 (m, 2H), 1.38 (br d, J=12 Hz, 2H).

EXAMPLE 45

1,1-Dioxido-2-(4-(4'-(3,4-dihydro-1-oxonapththalene)-2(1H)-spiropiperidin-1'-yl)butyl)-1,2-benzisothiazol-3(2H)-one

From 4'-(3,4-dihydro-1-oxonapththalene)-2(1H)-spiropiperidine, prepared as described by P. J. Gilligan, et al., *J. Med. Chem.* **1994**, *37*, 364-370, and 2-(4-bromobutyl)-1,1-dioxido-1,2-benzothiazol-3(2H)-one using the procedure described for Example 15, Step 5 there was obtained a white solid: mp 226-8°C.

EXAMPLE 46

4-(3,4-Dihydro-6-methyl-spiro[2H-1-benzopyran-2,4'-piperidine-4(3H)-one]-1'-yl)-butylphthalimide

From 3,4-dihydro-6-methyl-spiro[2H-1-benzopyran-2,4'-piperidine, and 2-(4-bromobutyl)-phthalimide using the procedure described for Example 15, Step 5 there was obtained a white solid:mp>275°C dec.

EXAMPLE 47

4-(Spiro(piperidine-4,6'-[6H]thieno[2,3-b]thiopyran-4'(5'H)-one-1'-yl)-butylphthalimide

From 4-(spiro(piperidine-4,6'-[6H]thieno[2,3-b]thiopyran-4'(5'H)-one, and 2-(4-bromobutyl)-phthalimide using the procedure described for Example 15, Step 5 there was obtained a white solid:mp 261-3°C dec.

EXAMPLE 48

4-(Spiro[benzothiazol-2(3H),4'-piperidin-1'-yl)-butylphthalimide

Step 1: A solution of 4-piperidone hydrochloride hydrate (2 gram, 13 mmol), bromobutylphthalimide (3.67 gram, 13 mmol) and triethylamine (3.4 ml, 26 mmol) in Chloroform (25 ml) was refluxed overnight. The reaction mixture was washed with sat. $NaHCO_3$ and was dried over Na_2SO_4. Purification using flash chromatography gave 4-(4'-ketopiperidinyl)butylphthalimide (0.85 gram).

Step 2: A solution of 4-(4'-ketopiperidinyl)butylphthalimide (200 mg, 0.67 mmol), 2-aminothiophenol (125ml, 0.73mmol) and tosic acid (30 mg) in benzene (25 ml) was refluxed overnight. The reaction mixture was concentrated and the residue was partitioned between ethyl acetate and sat. $NaHCO_3$. The organic layer was dried over Na_2SO_4. Chromatography gave a white solid: ^1H NMR (300 MHz, $CDCl_3$): 8.01-7.95 (m, 2H), 7.88-7.82 (m, 2H), 7.17 (d, J=7.57 Hz, 1H), 7.04 (t, 1H), 6.86 (t, J=3.76 Hz, 1H), 6.78 (d, J=7.63 Hz, 1H), 4.14 (br s, 1H), 3.85 (t, J=7.04 Hz, 2H), 2.89-2.06 (m, 2H), 2.54-2.30 (m, 6H), 2.18-2.06 (m, 2H), 1.90-1.72 (m, 2H), 1.69-1.37 (m, 2H).

EXAMPLE 49

4-(3,4-Dihydro-6-methoxy-spiro[2H-1-benzopyran-2,4'-piperidine-4(3H)-one]-1'-yl)-butylphthalimide

From 3,4-dihydro-6-methoxy-spiro[2H-1-benzopyran-2,4'-piperidine-4(3H)-one and 2-(4-bromobutyl)-phthalimide using the procedure described for Example 15, Step 5 there was obtained a white solid:mp 11-113°C.

EXAMPLE 50

4-(3,4-Dihydro-6-methanesulfonylamidyl-spiro[2H-1-benzopyran-2,4'-piperidine-4(3H)-one]-1'-yl)-butylphthalimide

From 3,4-dihydro-6-methanesulfonylamidyl-spiro[2H-1-benzopyran-2,4'-piperidine-4(3H)-one and 2-(4-bromobutyl)-phthalimide using the

procedure described for Example 15, Step 5 there was obtained a white solid: mp 89-90°C.

EXAMPLE 51

1,1-Dioxido-2-(4-(spiro[benzothiazol-2(3H),4'-piperidin-1'-yl)-butyl)-1,2-benzisothiazol-3(2H)-one

From 2-(4-bromobutyl)-1,1-dioxido-1,2-benzothiazol-3(2H)-one, 4-piperidone and 2-aminothiophenol using the procedure described for Example 48 there was obtained a white solid: mp 178-80°C.

EXAMPLE 52

4-(6-Trifluoromethyl-spiro[benzothiazol-2(3H),4'-piperidin-1'-yl)-butylphthalimide

From 4-(4'-ketopiperidinyl)butylphthalimide and 2-amino-5-trifluoromethylthiophenol using the procedure described for Example 48, Step 2 there was obtained a white solid: mp 157-8°C.

EXAMPLE 53

1,1-Dioxido-2-(4-(spiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-butyl)-1,2-benzisothiazol-3(2H)-one

From spiro[benzofuran-2(3H),4'-piperidine] prepared as described by R. C. Effland, et al. *J. Heterocyclic Chem.* **1981**, *18*, 811, and 2-(4-bromobutyl)-1,1-dioxido-1,2-benzothiazol-3(2H)-one using the procedure described for Example 15, Step 5 there was obtained a white solid: mp 98-100°C.

EXAMPLE 54

4-(Spiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-butylphthalimide

From spiro[benzofuran-2(3H),4'-piperidine] prepared as described by R. C. Effland, et al. *J. Heterocyclic Chem.* **1981**, *18*, 811, and 2-(4-bromobutyl)-phthalimide using the procedure described for Example 15, Step 5 there was obtained a white solid: mp 255-7°C.

EXAMPLE 55

4-(Spiro[2H-1,3-benzoxazine-2,4'-piperidin]-1'-yl)-butylphthalimide

From spiro[2H-1,3-benzoxazine-2,4'-piperidine] and 2-(4-bromobutyl)-phthalimide using the procedure described for Example 15, Step 5 there was obtained a white solid: mp 165-7°C.

EXAMPLE 56

3,3-Dioxido-1,2-dehydro-2-(4-(spiro[2H-indenyl-2,4'-piperidine-1(3H)-one]-1'-yl)-butyl)-naphth[1,2-d]isothiazol-1-one

From 1,3-dihydro-1-oxo-spiro(2H-indenyl-2,4'-piperidine) and 2-(4-bromobutyl)-3,3-dioxido-1,2-dehydronaphth[1,2-d]isothiazol-1-one using the procedure described for Example 15, Step 5 there was obtained a white solid: ^{1}H NMR (300 MHz, $CDCl_3$): 9.27 (d, J=8.4 Hz, 1H), 8.30 (d, J=8.5 Hz, 1H), 8.00 (d, J=7.6 Hz, 1H), 7.88 (d, J=8.5 Hz, 1H), 7.82-7.73 (m, 3H), 7.56 (t, 1H), 7.43 (d, J=7.6 Hz, 1H), 7.36 (t, 3H), 3.85 (t, J=7.4 Hz, 2H), 3.01 (s, 2H), 2.97 (br d, 2H), 2.14-2.0 (m, 4H), 1.90 (m, 8H), 1.69 (m, 2H), 1.38 (br d, J=12 Hz, 2H); mp (HCl salt) 243-5°C.

EXAMPLE 57

1,1-Dioxido-2-(4-(spiro[2H-indenyl-2,4'-piperidine-1(3H)-one]-1'-yl)-butyl)-4-methoxy-1,2-benzisothiazol-3(2H)-one

From 1,3-dihydro-1-oxo-spiro(2H-indenyl-2,4'-piperidine) and 1,1-dioxido-2-(4-bromobutyl)-4-methoxy-1,2-benzisothiazol-3(2H)-one using the procedure described for Example 15, Step 5 there was obtained a white solid: ^{1}H NMR (300 MHz, $CDCl_3$): 7.83-7.74 (m, 2H), 7.61 (t, J=7.4 Hz, 1H), 7.56 (m, 2H), 7.34 (t, J=7.7 Hz, 1H), 7.29 (m, 1H), 4.05 (s, 3H), 3.78 (t, J=7.3 Hz, 2H), 3.02 (s, 2H), 2.96 (br d, J=11 Hz, 2H), 2.43 (t, J=7.6 Hz, 2H), 2.17-2.0 (m, 4H), 1.87 (m, 2H), 1.65 (m, 2H), 1.31 (br d, J=12 Hz, 2H).

EXAMPLE 58

1,1-Dioxido-2-(4-(spiro[2H-indenyl-2,4'-piperidine-1(3H)-one]-1'-yl)-butyl)-7-methoxy-1,2-benzisothiazol-3(2H)-one

From 1,3-dihydro-1-oxo-spiro(2H-indenyl-2,4'-piperidine) and 1,1-dioxido-2-(4-bromobutyl)-7-methoxy-1,2-benzisothiazol-3(2H)-one using the procedure described for Example 15, Step 5 there was obtained a white solid: ^{1}H NMR (300 MHz, $CDCl_3$): 7.77-7.72 (m, 2H), 7.61-56 (m, 2H), 7.44 (d, J=7.6 Hz, 1H), 7.37 (t, 1H), 7.28 (d, 1H), 4.05 (s, 3H), 3.80 (t, J=7.3 Hz, 2H), 3.02 (s, 2H), 2.96 (m, 2H), 2.44 (t, J=7.5 Hz, 2H), 2.13-2.03 (m, 4H), 1.89 (m, 2H), 1.65 (m, 2H), 1.39 (br d, J=12 Hz, 2H); mp (HCl salt) 130°C (dec).

EXAMPLE 59

1,1-Dioxido-2-(4-(spiro(1,3-dihydro-1-oxo-2H-indenyl-2,4'-piperidin-1'-yl)butyl)-5-methoxy-1,2-benzisothiazol-3(2H)-one

From 1,3-dihydro-1-oxo-spiro(2H-indenyl-2,4'-piperidine) and 1,1-dioxido-2-(4-bromobutyl)-5-methoxy-1,2-benzisothiazol-3(2H)-one using the procedure described for Example 15, Step 5 there was obtained a white solid: ^{1}H NMR (400 MHz, $CDCl_3$): 7.80 (d, J=8.6 Hz, 1H), 7.75 (d, J=7.6 Hz, 1H), 7.6 (d, J=7.6 Hz, 1H), 7.59 (t, 1H), 7.48-7.37 (m, 2H), 7.32 (t, J=7.8 Hz, 1H), 7.29 (d, 1H), 3.95 (s, 3H), 3.81 (t, J=7.4 Hz, 2H), 3.02 (s, 2H), 2.95 (br d, J=11 Hz, 2H), 2.44 (t, J=7.4 Hz, 2H), 2.14-2.0 (m, 4H), 1.90 (m, 2H), 1.65 (m, 2H), 1.38 (br d, J=12 Hz, 2H); mp (HCl salt) 205-7°C.

EXAMPLE 60

1,1-Dioxido-2-(4-(spiro(1,3-dihydro-1-oxo-2H-indenyl-2,4'-piperidin-1'-yl)butyl)-6-methoxy-1,2-benzisothiazol-3(2H)-one

From 1,3-dihydro-1-oxo-spiro(2H-indenyl-2,4'-piperidine) and 1,1-dioxido-2-(4-bromobutyl)-6-methoxy-1,2-benzisothiazol-3(2H)-one

using the procedure described for Example 15, Step 5 there was obtained a white solid:rom spiro[2H-indene-2,4'-piperidine and 2-(4-bromobutyl)-5-methoxy-1,2-benzisothiazol-3(2H)-one using the procedure described for Example 15, Step 5 there was obtained a white solid: ^{1}H NMR (400 MHz, $CDCl_3$): 7.94 (d, J=8.6 Hz, 1H), 7.75 (d, J=7.6 Hz, 1H), 7.6 (t, 1H), 7.44 (d, J=7.6 Hz, 1H), 7.39-7.34 (m, 2H), 7.27-7.25 (m, 1H), 3.97 (s, 3H), 3.79 (t, J=7.3 Hz, 2H), 3.02 (s, 2H), 2.96 (m, 2H), 2.44 (br t, 2H), 2.14-2.0 (m, 4H), 1.89 (m, 2H), 1.65 (m, 2H), 1.38 (br d, 2H); mp (HCl salt) 229-31°C.

EXAMPLE 61

1,1-Dioxido-2-(4-(spiro(1,3-dihydro-1-oxo-2H-indenyl-2,4'-piperidin-1'-yl)butyl)-5-methyl-1,2-benzisothiazol-3(2H)-one

From 1,3-dihydro-1-oxo-spiro(2H-indenyl-2,4'-piperidine) and 1,1-dioxido-2-(4-bromobutyl)-5-methyl-1,2-benzisothiazol-3(2H)-one using the procedure described for Example 15, Step 5 there was obtained a white solid: ^{1}H NMR (300 MHz, $CDCl_3$): 7.86-7.76 (m, 3H), 7.68-7.58 (m, 2H), 7.46 (d, J= 6.8 Hz, 1H), 7.39 (t, J=7.4 Hz, 1H), 3.83 (t, J=6.8 Hz, 2H), 3.03 (s, 2H), 2.98 (br d, J=10.6 Hz, 2H), 2.57 (s, 3H), 2.46 (t, J=7.4 Hz, 2H), 2.19-2.05 (m, 4H), 1.92 (m, 2H), 1.66 (m,2H), 1.40 (br d, 11.6 Hz, 2H); mp (HCl salt) 230-1°C.

EXAMPLE 62

1,1-Dioxido-2-(4-(spiro(1,3-dihydro-1-oxo-2H-indenyl-2,4'-piperidin-1'-yl)butyl)-5-chloro-1,2-benzisothiazol-3(2H)-one

From 1,3-dihydro-1-oxo-spiro(2H-indenyl-2,4'-piperidine) and 1,1-dioxido-2-(4-bromobutyl)-5-chloro-1,2-benzisothiazol-3(2H)-one using the procedure described for Example 15, Step 5 there was obtained a white solid: ^{1}H NMR (400 MHz, $CDCl_3$): 8.02 (s, 1H), 7.87-7.80 (m, 2H), 7.75 (d, J=7.6 Hz, 1H), 7.59 (t, J=7.6 Hz, 1H), 7.44 (d, J=7 Hz, 1H), 7.37 (t, J=7.5 Hz, 1H), 3.82 (t, J=7.4 Hz, 2H), 3.02 (s, 2H), 2.95

(br d, J=11.5 Hz, 2H), 2.44 (t, 2H), 2.16-2.0 (m, 4H), 1.90 (m, 2H), 1.64 (m, 2H), 1.38 (br d, J=11.5 Hz, 2H); mp (HCl salt) 235-7°C.

EXAMPLE 63

1,1-Dioxido-2-(4-(spiro(1,3-dihydro-1-oxo-2H-indene-2,4'-piperidin-1'-yl)butyl)-5-fluoro-1,2-benzisothiazol-3(2H)-one

From 1,3-dihydro-1-oxo-spiro(2H-indenyl-2,4'-piperidine) and 1,1-dioxido-2-(4-bromobutyl)-5-fluoro-1,2-benzisothiazol-3(2H)-one using the procedure described for Example 15, Step 5 there was obtained a white solid: ^{1}H NMR (400 MHz, $CDCl_3$): 7.93 (m, 1H), 7.76-7.71 (m, 2H), 7.61-7.45 (m, 2H), 7.44 (d, J=7.7 Hz, 1H), 7.37 (t, J=7.4 Hz, 1H), 3.82 (t, J=7.4 Hz, 2H), 3.02 (s, 2H), 2.97 (br d, J=11.5 Hz, 2H), 2.45 (t, J=7.4 Hz, 2H), 2.16 (m, 2H), 2.05 (m, 2H), 1.95-1.87 (m, 2H), 1.7-1.6 (m, 2H), 1.38 (br d, J=12.5 Hz, 2H); mp (HCl salt) 238-40°C.

EXAMPLE 64

1,1-Dioxido-2-(4-(spiro(1,3-dihydro-1-oxo-2H-indenyl-2,4'-piperidin-1'-yl)butyl)-5-nitro-1,2-benzisothiazol-3(2H)-one

From 1,3-dihydro-1-oxo-spiro(2H-indenyl-2,4'-piperidine) and 1,1-dioxido-2-(4-bromobutyl)-5-nitro-1,2-benzisothiazol-3(2H)-one using the procedure described for Example 15, Step 5 there was obtained a white solid: ^{1}H NMR (400 MHz, $CDCl_3$): 8.84 (s, 1H), 8.70 (d, J=6.38 Hz, 1H), 8.11 (d, J=8.4 Hz, 1H), 7.73 (d, J=7.6 Hz, 1H), 7.56 (d, J=8.4 Hz, 1H), 7.43 (d, J=7.7 Hz, 1H), 7.35 (t, 1H), 3.86 (t, J=7.4 Hz, 2H), 3.00 (s, 2H), 2.95 (br d, 2H), 2.42 (t, J=7.4 Hz, 2H), 2.14 (m, 2H), 2.04 (m, 2H), 1.94 (m, 2H), 1.63 (m, 2H), 1.37 (br d, J=12.5 Hz, 2H); mp (HCl salt) 241-3°C.

EXAMPLE 65

1,1-Dioxido-2-(4-(spiro(1,3-dihydro-1-oxo-2H-indenyl-2,4'-piperidin-1'-yl)butyl)-6-nitro-1,2-benzisothiazol-3(2H)-one

From 1,3-dihydro-1-oxo-spiro(2H-indenyl-2,4'-piperidine) and 1,1-dioxido-2-(4-bromobutyl)-6-nitro-1,2-benzisothiazol-3(2H)-one using the procedure described for Example 15, Step 5 there was obtained a white solid: ^{1}H NMR (300 MHz, $CDCl_3$): 8.75 (s, 1H), 8.68 (dd, J= 2, 6.4 Hz, 1H), 8.26 (d, J=8.3 Hz, 1H), 7.75 (d, J= 7.5 Hz, 1H), 7.59 (t, 1H), 4.25 (br d, J=12.5 Hz, 2H), 3.88 (t, J=7.4 Hz, 2H), 3.02 (s, 2H), 2.96 (br d, 2H), 2.44 (t, J=7.4 Hz, 2H), 2.13-1.91 (m, 6H), 1.63 (m, 2H); mp (HCl salt) 231-4°C.

EXAMPLE 66

1,1-Dioxido-2-(4-(spiro(1,3-dihydro-1-oxo-2H-indenyl-2,4'-piperidin-1'-yl)butyl)-isothiazolo[5,4-c]pyridin-3(2H)-one

Step 1: A solution of 16 g of pyridine-3-sulfonyl chloride prepared as described by B. I. Alo, O. B. Familoni, F. Marsais and G. Queguiner, *J. Heterocyclic Chem.* **1992**, *29*, 61-4 in 250 mL of chloroform was added to a solution of 8 g of 4-amino-1-butanol and 40 mL of triethylamine in 250 mL of chloroform at 0°C. The mixture was stirred overnight while warming to ambient temperature, the concentrated under reduced pressure to dryness. The residue was stirred with 500 mL of ethyl acetate, filtered and concentrated to dryness. To a solution of the crude N-(4-hydroxybutyl)pyridine-3-sulfonamide (28 g) in 200 mL of dichloromethane was added 30 mL of 3,4-dihydro-2H-pyran and 3 g of p-toluenesulfonic acid monohydrate. The reaction was stirred overnight, shaken with 100 mL of saturated sodium bicarbonate, dried over MgSO4, and concentrated to dryness. Chromatography of the residue over silica gel, eluting with ethyl acetate gave 20 g of N-(4-(2-tetrahydropyranyloxy)butyl)pyridine-3-sulfonamide as a thich amber oil.

Step 2: To a stirred solution of 54 mL of dry diisopropylamine in 200 mL of dry tetrahydrofuran cooled to -78°C was added 205 mL of commercial 1.6M n-butyllithium in hexane keeping the temperature below -30°C. After aging for 30 min -30°C, the solution was cooled to -78°C a solution of 23.3 g of N-(4-(2-tetrahydropyranyloxy)butyl) pyridine-3-sulfonamide in 150 mL of dry tetrahydrofuran was added dropwise keeping the internal temperature below -70°C (ca. 30 min). The resulting solution was aged at -78°C for 2.5 h and the deep red solution quenched by a stream of carbon dioxide gas with a fritted glass dispersion tube. During the addition, the color dissipated and the temperature rose to -40°C. After 15 min below -40°C, the bath was removed and the solution allowed to warm to room temprature over 1 h under a gentle stream of carbon dioxide. The mixture was partitioned between 400 mL of water and 500 mL of ether. The ether extracts contained unreacted N-(4-(2-tetrahydropyranyloxy)butyl) pyridine-3-sulfonamide. The aqueous layer was carefully acidified to pH=3 with concentrated HCl, and extracted with five 200 mL portions of chloroform. The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. Drying under vacuum gave 19 g of N-(4-(2-tetrahydropyranyloxy)butyl) 4-carboxypyridine-3-sulfonamide as a amber solid.

Step 3: To a stirred solution of 19 g of N-(4-(2-tetrahydropyranyloxy)butyl) 4-carboxypyridine-3-sulfonamide and 16 mL of triethylamine in 300 mL of dichloromethane at 0°C was added 6.5 mL of methyl chloroformate dropwise. After 30 min, the mixture was shaken with 100 mL of saturated sodium bicarbonate, dried over $MgSO_4$ and concentrated under reduced pressure. Chromatography of the dark brown oil over silica gel, eluting with 1:1 ethyl acetate: hexane gave 16 g of homogeneous 1,1-dioxido-2-(4-(2-tetrahydropyranyloxy) butyl)-isothiazolo[5,4-c]pyridin-3(2H)-one as an amber oil.

Step 4: A solution of 1 g of 2-(4-(2-tetrahydropyranyloxy)butyl)-isothiazolo[5,4-c]pyridin-3(2H)-one and 0.1 g of p-toluenesulfonic acid monohydrate in 50 mL of methanol was stirred overnight at ambient

temperature and concentrated to dryness under reduced pressure. The residue was dissolved in 200 mL of ethyl acetate, washed with 4 mL of saturated sodium bicarbonate, dried over MgSO4 and concentrated under reduced pressure. Drying under vacuum overnight gave 0.73 g (78%) of 2-(4-hydroxybutyl)-isothiazolo[5,4-c]pyridin-3(2H)-one as an oil: ^{1}H NMR (400 MHz, $CDCl_3$): 9.28 (s, 1H), 9.15 (d, J=5 Hz, 1H), 7.98 (d, J=5Hz, 1H), 3.86 (t, J= 7.5 Hz, 2H), 3.71 (t, J= 6.4 Hz, 2H), 2.36 (br s, 1H), 1.98 (m, 2H), 1.27 (m, 2H).

Step 4: To a stirred solution of 0.73 g of 2-(4-hydroxybutyl)-isothiazolo[5,4-c]pyridin-3(2H)-one and 0.8 mL of triethylamine in 50 mL of dry tetrahydrofuran at 0°C was added 0.63 g of technical grade 4-nitrobenzenesulfonyl chloride. After 4 h, the solution was filtered and concentrated to dryness under reduced pressure. The residue was dissolved in 100 mL of ethyl acetate, washed with 10 mL of saturated sodium carbonate and dried over $MgSO_4$. Concentration under reduced pressure gave 1.4 g of crude 2-(4-(4-nitrobenzenesulfonyloxy)butyl)-isothiazolo[5,4-c]pyridin-3(2H)-one as an oil. The crude product was a mixture of 4-nitrobenzenesulfonate contaminated with a small amount of chloride by NMR, and was used in the next step without further purification.

Step 6: A mixture of 0.60 g of 1,3-dihydro-1-oxo-spiro(2H-indenyl-2,4'-piperidine) and 1.4 g of 1,1-dioxido-2-(4-(4-nitrobenzenesulfonyloxy)butyl)-isothiazolo[5,4-c]pyridin-3(2H)-one in 20 mL of anhydrous acetonitrile were allowed to stir overnight at ambient temperature then concentrated to dryness under reduced pressure. The solid mass was partitioned between 200 mL of ethyl acetate and 20 mL of saturated sodium carbonate. The organic extract was dried over MgSO4 and concentrated under reduced pressure. Chromatography of the residue on silica gel, eluting with 10% methanol in ethyl acetate gave 0.5 g of a white solid: ^{1}H NMR (400 MHz, $CDCl_3$): 9.26 (s, 1H), 9.15 (m, 1H), 7.95 (d, J=4.9 Hz, 1H), 7.75 (d, J= 7.5 Hz, 1H), 7.59 (t, J=8.1 Hz, 1H), 7.44 (d, J=7.7 Hz, 1H), 3.85 (t, J=7.4 Hz, 2H), 3.02 (s, 2H), 2.95 (br d, J=12 Hz, 2H), 2.44 (t, J=7.4

Hz, 2H), 2.17-2.03 (m, 4H), 1.92 (m, 2H), 1.64 (m, 2H), 1.4 (br d, J=12 Hz, 2H); mp (HCl salt) 228-30°C.

EXAMPLE 67

1,1-Dioxido-2-(4-(spiro(1,3-dihydro-1-oxo-2H-indenyl-2,4'-piperidin-1'-yl)butyl)-isothiazolo[5,4-b]pyridin-3(2H)-one

Step 1: Chlorine gas was dispersed through a mixture of 4.3 g of methyl 2-mercaptonicotinate, prepared as described by L. Katz, W. Schroeder and M. Cohen, *J. Org. Chem.* **1954**, *19*, 711-17, 10 mL of dichloromethane, 60 mL of glacial acetic acid and 150 mL of water at 0-3°C for 1.5 h. The resulting solution was extracted with four 200 mL portions of chloroform and the combined extracts dried over $MgSO_4$ and concentrated under reduced pressure in a fume hood. The oily methyl 2-chlorosulfonylnicotinate, 3.5 g, was dissolved in 20 mL of dichloromethane and added to a solution of 2 g of 4-amino-1-butanol and 3 mL of triethylamine in 200 mL of dichloromethane at 0°C. The mixture was stirred overnight while warming to ambient temperature, the decanted and the residue extracted with three 100 mL portions of dichloromethane. The combined extracts were concentrated under reduced pressure to dryness. To a solution of the resulting crude N-(4-hydroxybutyl) 3-methoxycarbonylpyridine-2-sulfonamide (5 g) in 100 mL of dichloromethane was added 10 mL of 3,4-dihydro-2H-pyran and 1 g of p-toluenesulfonic acid monohydrate. The reaction was stirred overnight, shaken with 50 mL of saturated sodium bicarbonate, dried over $MgSO_4$, and concentrated to dryness. To a stirred solution of the resulting crude N-(4-(2-tetrahydropyranyloxy)butyl) 3-methoxycarbonylpyridine-2-sulfonamide (7 g) in 100 mL of 100 mL of methanol and 30 mL of water was added 2 g of lithium hydroxide monohydrate. The reaction mixture was stirred overnight at ambient temperature, concentrated to dryness under reduced pressure to remove methanol, acidified to pH=3 with concentrated HCl and extracted with five 50 mL portions

of chloroform. The combined extracts were dried over MgSO4 and concentrated to dryness. The residue, N-(4-(2-tetrahydropyranyloxy)butyl) 3-carboxycarbonylpyridine-2-sulfonamide weighed 5 g and was used without further purification.
Step 2: To a stirred solution of 3 g of N-(4-(2-tetrahydropyranyloxy)butyl) 3-carboxycarbonylpyridine-2-sulfonamide and 2.3 mL of triethylamine in 100 mL of dichloromethane at 0°C was added 0.8 mL of methyl chloroformate dropwise. After 2 h, the mixture was shaken with 10 mL of saturated sodium bicarbonate, dried over $MgSO_4$ and concentrated under reduced pressure. Chromatography of the dark brown oil over silica gel, eluting with 1:1 ethyl acetate: hexane gave 3 g of homogeneous 1,1-dioxido-2-(4-(2-tetrahydropyranyloxy)butyl)-isothiazolo[5,4-b]pyridin-3(2H)-one as an amber oil.
Step 3: A solution of 1 g of 2-(4-(2-tetrahydropyranyloxy)butyl)-isothiazolo[5,4-b]pyridin-3(2H)-one and 0.1 g of p-toluenesulfonic acid monohydrate in 50 mL of methanol was stirred overnight at ambient temperature and concentrated to dryness under reduced pressure. The residue was dissolved in 200 mL of ethyl acetate, washed with 4 mL of saturated sodium bicarbonate, dried over MgSO4 and concentrated under reduced pressure. Drying under vacuum overnight gave 0.73 g of 1,1-dioxido-2-(4-hydroxybutyl)-isothiazolo[5,4-b]pyridin-3(2H)-one as an oil: ^1H NMR (400 MHz, $CDCl_3$): 9.00 (d, J=1.5 Hz, 1H), 8.40 (d, J= 7.7 Hz, 1H), 7.80 (dd, J=1.5, 7.7 Hz, 1H), 3.86 (t, J= 7.5 Hz, 2H), 3.71 (t, J= 6.4 Hz, 2H), 2.31 (br s, 1H), 1.98 (m, 2H), 1.26 (m, 2H).
Step 4: To a stirred solution of 0.73 g of 1,1-dioxido-2-(4-hydroxybutyl)-isothiazolo[5,4-b]pyridin-3(2H)-one and 0.8 mL of triethylamine in 50 mL of dry tetrahydrofuran at 0°C was added 0.63 g of technical grade 4-nitrobenzenesulfonyl chloride. After 4 h, the solution was filtered and concentrated to dryness under reduced pressure. The residue was dissolved in 100 mL of ethyl acetate, washed with 10 mL of saturated sodium carbonate and dried over $MgSO_4$. Concentration under reduced pressure gave 1.4 g of crude

1,1-dioxido-2-(4-(4-nitrobenzenesulfonyloxy)butyl)-isothiazolo[5,4-b]pyridin-3(2H)-one as an oil. The crude product was a mixture of 4-nitrobenzenesulfonate contaminated with a small amount of chloride by NMR, and was used in the next step without further purification. Step 5: A mixture of 0.60 g of 1,3-dihydro-1-oxo-spiro(2H-indenyl-2,4'-piperidine) and 1.4 g of 1,1-dioxido-2-(4-(4-nitrobenzenesulfonyloxy)butyl)-isothiazolo[5,4-b]pyridin-3(2H)-one in 20 mL of anhydrous acetonitrile were allowed to stir overnight at ambient temperature then concentrated to dryness under reduced pressure. The solid mass was partitioned between 200 mL of ethyl acetate and 20 mL of saturated sodium carbonate. The organic extract was dried over MgSO4 and concentrated under reduced pressure. Chromatography of the residue on silica gel, eluting with 10% methanol in ethyl acetate gave 0.5 g of a white solid: ^{1}H NMR (400 MHz, $CDCl_3$): 9.00(d, J=4.8 Hz, 1H), 8.38 (d, J=7.7 Hz, 1H), 7.81-7.74 (m, 2H), 7.59 (t, J= 7.4 Hz, 1H), 7.45 (d, J=7 Hz, 1H), 7.37 (t, J=7.4 Hz, 1H), 3.87 (t, J=7.23 Hz, 1H), 3.02 (s, 2H), 2.97 (br d, J=11.35 Hz, 2H), 2.46 (t, J=7.33 Hz, 2H), 2.20-2.03 (m, 4H), 2.07-2.20 (m, 2H), 1.97-1.90 (m, 2H), 1.70-1.61 (m, 2H), 1.61 (br d, J=12.08 Hz, 2H).

EXAMPLE 68

1,1-Dioxido-2-(4-(4-(6-methyl-2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-5-nitro-1,2-benzisothiazol-3(2H)-one

From 4-(6-methyl-2-oxo-3-benzoxazolinyl)-piperidine and 2-(4-bromobutyl)-1,1-dioxido-5-nitro-1,2-benzisothiazol-3(2H)-one using the procedure described for Example 15, Step 5 there was obtained a white solid: ^{1}H NMR, HCl salt, (400 MHz, $CDCl_3$): 8.87 (d, J = 2.0 Hz, 1H), 8.74 (d, J = 2.18 Hz, 1H), 8.72 (d, J = 1.8 Hz, 1H), 8.14 (d, J = 8.4 Hz, 1H), 7.11 (d, J = 6.54 Hz, 1H), 7.03 (s, 1H), 6.94 (d, J = 8.06 Hz, 1H), 4.18 (m, 1H), 3.89 (t, J = 7.39 Hz, 2H), 3.06 (d, J = 10.07 Hz, 2H), 2.46 (m, 2H), 2.38 (s, 3H), 2.34 (m, 2H), 2.14 (t, J = 11.5 Hz, 2H), 1.94 (m, 2H), 1.85 (d, J = 11.4 Hz, 2H), 1.65 (m, 2H).

EXAMPLE 69

2-(4-(Spiro(1,3-dihydro-1-oxo-2H-indenyl-2,4'-piperidin-1'-yl)butyl)-pyrrolo[3,4b]pyridin-5,7(1H)-dione

From 1,3-dihydro-1-oxo-spiro(2H-indenyl-2,4'-piperidine) and 2-(4-bromobutyl)-pyrrolo[3,4b]pyridin-5,7(1H)-dione using the procedure described for Example 15, Step 5 there was obtained a white solid: ^{1}H NMR, (400 MHz, $CDCl_3$): 9.15 (s, 1H), 9.06 (s, 1H), 9.06 (d, J=4.76 Hz, 1H), 7.75 (d, J=4.76 Hz, 1H), 7.59 (t, J=7.42 Hz, 1H), 7.44 (d, J=8.0Hz, 1H), 7.37 (t, J=7.33 Hz, 1H), 3.76 (t, J=7.14 Hz, 2H), 3.02 (s, 2H), 2.41 (br t, J=7.33 Hz, 2H), 2.12-1.99 (m, 4H), 1.77-1.72 (m, 2H), 1.56 (br m, 2H), 1.38 (m, 2H).

EXAMPLE 70

1,1-Dioxido-2,3-dihydro-2-(4-(spiro[2H-indenyl-2,4'-piperidine-1(3H)-one]-1'-yl)-butyl)-naphth[1,8-de]isothiazin-3-one

From 1,3-dihydro-1-oxo-spiro(2H-indenyl-2,4'-piperidine) and 2-(4-bromobutyl)-1,1-dioxido-2,3-dihydronaphth[1,8-de]isothiazin-3-one using the procedure described for Example 15, Step 5 there was obtained a white solid: ^{1}H NMR (300 MHz, $CDCl_3$): 8.37 (d, J=7.92 Hz, 1H), 8.26 (d, 1H), 8.08 (m, 2H), 7.86-7.74 (m, 3H), 7.58 (t, 1H), 7.44 (d, J=7.7 Hz, 1H), 7.38 (t, 1H), 3.90 (t, J=7.3 Hz, 2H), 3.02 (s, 2H), 2.98 (br d, 2H), 2.46 (t, J=7.4 Hz, 2H), 2.14-1.94 (m, 6H), 1.69 (m, 2H), 1.40 (br d, 2H); mp (HCl salt) 248-50°C.

EXAMPLE 71

2-(4-Bromobutyl)-1,1-dioxido-4-methoxy-1,2-benzothiazol-3(2H)-one

The general procedure of J. D. Commerford and H. B. Donahue *J. Org. Chem.* **1956**, *21*, 583-4 was modified: A mixture of 0.5 g of 3,3-dioxido-4-methoxy-1,2-benzothiazol-3(2H)-one prepared as described by D. J. Hlasta, J. J. Court and R. C. Desai, *Tetrahedron Lett.* **1991**, *32*, 7179-82, 1 mL of N,N-dimethylformamide and 0.1

g of sodium hydride 60% oil dispersion was stirred at ambient temperature for 15 min, and 1.4 mL of 1,4-dibromobutane was added. After stirring at ambient temperature overnight, the mixture was diluted with 25 mL of ethyl acetate, washed with 25 mL of sat'd $NaHCO_3$, 25 mL of sat'd brine and dried over $MgSO_4$. Removal of solvents under reduced pressure and vacuum distillation gave a crude product as a viscous oil which was free of 1,4-dibromobutane by ^1H-NMR and was used without further purification.

EXAMPLE 72

2-(4-Bromobutyl)-1,1-dioxido-6-methoxy-1,2-benzothiazol-3(2H)-one

The general procedure of J. D. Commerford and H. B. Donahue *J. Org. Chem.* **1956**, *21*, 583-4 was modified: A mixture of 0.5 g of 3,3-dioxido-6-methoxy-1,2-benzothiazol-3(2H)-one prepared from N,N-diethyl-4-methoxybenzamide using the general procedure described by D. J. Hlasta, J. J. Court and R. C. Desai, *Tetrahedron Lett.* **1991**, *32*, 7179-82, 1 mL of N,N-dimethylformamide and 0.1 g of sodium hydride 60% oil dispersion was stirred at ambient temperature for 15 min, and 1.4 mL of 1,4-dibromobutane was added. After stirring at ambient temperature overnight, the mixture was diluted with 25 mL of ethyl acetate, washed with 25 mL of sat'd $NaHCO_3$, 25 mL of sat'd brine and dried over $MgSO_4$. Removal of solvents under reduced pressure and vacuum distillation gave a crude product as a viscous oil which was free of 1,4-dibromobutane by ^1H-NMR and was used without further purification.

EXAMPLE 73

2-(4-Bromobutyl)-1,1-dioxido-7-methoxy-1,2-benzothiazol-3(2H)-one

The general procedure of J. D. Commerford and H. B. Donahue *J. Org. Chem.* **1956**, *21*, 583-4 was modified: A mixture of 0.5 g of

3,3-dioxido-7-methoxy-1,2-benzothiazol-3(2H)-one prepared from N,N-diethyl-3-methoxybenzamide using the general procedure described by D. J. Hlasta, J. J. Court and R. C. Desai, *Tetrahedron Lett.* **1991**, *32*, 7179-82, 1 mL of N,N-dimethylformamide and 0.1 g of sodium hydride 60% oil dispersion was stirred at ambient temperature for 15 min, and 1.4 mL of 1,4-dibromobutane was added. After stirring at ambient temperature overnight, the mixture was diluted with 25 mL of ethyl acetate, washed with 25 mL of sat'd $NaHCO_3$, 25 mL of sat'd brine and dried over $MgSO_4$. Removal of solvents under reduced pressure and vacuum distillation gave a crude product as a viscous oil which was free of 1,4-dibromobutane by ^1H-NMR and was used without further purification.

EXAMPLE 74

2-(4-Bromobutyl)-1,1-dioxido-5-methyl-1,2-benzothiazol-3(2H)-one

The general procedure of J. D. Commerford and H. B. Donahue *J. Org. Chem.* **1956**, *21*, 583-4 was modified: A mixture of 0.5 g of 3,3-dioxido-5-methyl-1,2-benzothiazol-3(2H)-one prepared as described by J. G. Lombardino, *J. Org. Chem.* **1971**, *36*, 1843-5, 1 mL of N,N-dimethylformamide and 0.1 g of sodium hydride 60% oil dispersion was stirred at ambient temperature for 15 min, and 1.4 mL of 1,4-dibromobutane was added. After stirring at ambient temperature overnight, the mixture was diluted with 25 mL of ethyl acetate, washed with 25 mL of sat'd $NaHCO_3$, 25 mL of sat'd brine and dried over $MgSO_4$. Removal of solvents under reduced pressure and vacuum distillation gave a crude product as a viscous oil which was free of 1,4-dibromobutane by ^1H-NMR and was used without further purification.

EXAMPLE 75

2-(4-Bromobutyl)-1,1-dioxido-5-fluoro-1,2-benzothiazol-3(2H)-one

The general procedure of J. D. Commerford and H. B. Donahue *J. Org. Chem.* **1956**, *21*, 583-4 was modified: A mixture of 0.5 g of 3,3-dioxido-5-fluoro-1,2-benzothiazol-3(2H)-one prepared as described by J. G. Lombardino, *J. Org. Chem.* **1971**, *36*, 1843-5, 1 mL of N,N-dimethylformamide and 0.1 g of sodium hydride 60% oil dispersion was stirred at ambient temperature for 15 min, and 1.4 mL of 1,4-dibromobutane was added. After stirring at ambient temperature overnight, the mixture was diluted with 25 mL of ethyl acetate, washed with 25 mL of sat'd $NaHCO_3$, 25 mL of sat'd brine and dried over $MgSO_4$. Removal of solvents under reduced pressure and vacuum distillation gave a crude product as a viscous oil which was free of 1,4-dibromobutane by ^{1}H-NMR and was used without further purification.

EXAMPLE 76

2-(4-Bromobutyl)-1,1-dioxido-5-chloro-1,2-benzothiazol-3(2H)-one

The general procedure of J. D. Commerford and H. B. Donahue *J. Org. Chem.* **1956**, *21*, 583-4 was modified: A mixture of 0.5 g of 3,3-dioxido-5-chloro-1,2-benzothiazol-3(2H)-one prepared as described by J. G. Lombardino, *J. Org. Chem.* **1971**, *36*, 1843-5, 1 mL of N,N-dimethylformamide and 0.1 g of sodium hydride 60% oil dispersion was stirred at ambient temperature for 15 min, and 1.4 mL of 1,4-dibromobutane was added. After stirring at ambient temperature overnight, the mixture was diluted with 25 mL of ethyl acetate, washed with 25 mL of sat'd $NaHCO_3$, 25 mL of sat'd brine and dried over $MgSO_4$. Removal of solvents under reduced pressure and vacuum distillation gave a crude product as a viscous oil which

was free of 1,4-dibromobutane by ^{1}H-NMR and was used without further purification.

EXAMPLE 77

2-(4-Bromobutyl)-1,1-dioxido-6-nitro-1,2-benzothiazol-3(2H)-one

The general procedure of J. D. Commerford and H. B. Donahue *J. Org. Chem.* **1956**, *21*, 583-4 was modified: A stirred mixture of 1.0 g of 3,3-dioxido-6-nitro-1,2-benzothiazol-3(2H)-one prepared as described by H. Kamogawa, S. Yamamoto and M. Nanasawa, *Bull. Chem. Soc. Japan* ,**1982**, *55*, 3824-7, and 6 mL of 1N NaOH was warmed to dissolution and allowed to cool to ambient temperature for 15 min. The mixture was concentrated to dryness under reduced pressure and the white solid azeotropically dried with 20 mL of toluene. The resulting sodium salt was dissolved in 3 mL of N,N-dimethylformamide and 2.6 mL of 1,4-dibromobutane was added. After stirring at ambient temperature overnight, the mixture was diluted with 25 mL of ethyl acetate, washed with 25 mL of sat'd $NaHCO_3$, 25 mL of sat'd brine and dried over $MgSO_4$. Removal of solvents under reduced pressure and vacuum distillation gave a crude product as a solid which was free of 1,4-dibromobutane by ^{1}H-NMR and was used without further purification.

EXAMPLE 78

2-(4-Bromobutyl)-1,1-dioxido-2,3-dihydronaphth[1,8-de] isothiazin-3-one

The general procedure of J. D. Commerford and H. B. Donahue *J. Org. Chem.* **1956**, *21*, 583-4 was modified: A mixture of 0.5 g of 1,1-dioxido-2,3-dihydronaphth[1,8-de]isothiazin-3-one prepared as described by J. G. Lombardino, *J. Org. Chem.* **1971**, *36*, 1843-5, 1 mL of N,N-dimethylformamide and 0.1 g of sodium hydride 60% oil dispersion was stirred at ambient temperature for 15 min, and 1.4 mL

of 1,4-dibromobutane was added. After stirring at ambient temperature overnight, the mixture was diluted with 25 mL of ethyl acetate, washed with 25 mL of sat'd $NaHCO_3$, 25 mL of sat'd brine and dried over $MgSO_4$. Removal of solvents under reduced pressure and vacuum distillation gave a crude product as a viscous oil which was free of 1,4-dibromobutane by ^{1}H-NMR and was used without further purification.

EXAMPLE 79

2-(4-Bromobutyl)-3,3-dioxido-1,2-dehydronaphth[1,2-d] isothiazol-1-one

The general procedure of J. D. Commerford and H. B. Donahue *J. Org. Chem.* **1956**, *21*, 583-4 was modified: A mixture of 0.5 g of 3,3-dioxido-1,2-dehydronaphth[1,2-d]isothiazol-1-one prepared as described by J. G. Lombardino, *J. Org. Chem.* **1971**, *36*, 1843-5, 1 mL of N,N-dimethylformamide and 0.1 g of sodium hydride 60% oil dispersion was stirred at ambient temperature for 15 min, and 1.4 mL of 1,4-dibromobutane was added. After stirring at ambient temperature overnight, the mixture was diluted with 25 mL of ethyl acetate, washed with 25 mL of sat'd $NaHCO_3$, 25 mL of sat'd brine and dried over $MgSO_4$. Removal of solvents under reduced pressure and vacuum distillation gave a crude product as a viscous oil which was free of 1,4-dibromobutane by ^{1}H-NMR and was used without further purification.

EXAMPLE 80

2-(4-Bromobutyl)-pyrrolo[3,4b]pyridin-5,7(1H)-dione

The general procedure of J. D. Commerford and H. B. Donahue *J. Org. Chem.* **1956**, *21*, 583-4 was modified: A mixture of 0.5 g of commercial pyrrolo[3,4b]pyridin-5,7(1H)-dione (Aldrich Chemical Co.), 1 mL of N,N-dimethylformamide and 0.1 g of sodium hydride

60% oil dispersion was stirred at ambient temperature for 15 min, and 1.4 mL of 1,4-dibromobutane was added. After stirring at ambient temperature overnight, the mixture was diluted with 25 mL of ethyl acetate, washed with 25 mL of sat'd $NaHCO_3$, 25 mL of sat'd brine and dried over $MgSO_4$. Removal of solvents under reduced pressure and vacuum distillation gave a crude product as a viscous oil which was free of 1,4-dibromobutane by ^{1}H-NMR and was used without further purification.

EXAMPLE 81

1,1-Dioxido-2-(4-(spiro[3-oxo-phthalan-1,4'-piperidin-1'-yl)butyl)-1,2-benzisothiazol-3(2H)-one

From spiro[phthalan-1,4'-piperidine]-3-one, prepared as described in US Patent 3,686,186, and 2-(4-bromobutyl)-1,1-dioxido-1,2-benzothiazol-3(2H)-one using the procedure described for Example 15, Step 5 there was obtained a white solid: mp 226-8°C.

EXAMPLE 82

5-chloro-1-(4-piperidinyl)-3-benzoxazolin-2-one

From the reaction of 2-amino-4-chlorophenol and N-t-butyloxycarbonyl-4-piperidone according to Example 15 Steps 2-4 was obtained a white solid.

EXAMPLE 83

4-(3a-(R)-8a-(S)-2-oxo-3,3a,8,8a-tetrahydro-2H-indeno[1,2-d]oxazolinyl)-piperidine

From the reaction of (-)-1(S)-amino-2(R)-hydroxyindan, prepared according to W. J. Thompson et. al. *J. Med. Chem.* **1992**, *35*, 1685-1701, and N-t-butyloxycarbonyl-4-piperidone according to Example 15 Steps 2-4 was obtained a white solid.

EXAMPLE 84

4-(2-oxonaphth[2,3-d]oxazolinyl)-piperidine

From the reaction of 3-amino-2-naphthol and N-t-butyloxycarbonyl-4-piperidone according to Example 15 Steps 2-4 was obtained a white solid.

EXAMPLE 85

4-(6-methyl-2-oxo-3-benzoxazolinyl)-piperidine

From the reaction of 6-amino-m-cresol and N-t-butyloxycarbonyl-4-piperidone according to Example 15 Steps 2-4 was obtained a white solid.

EXAMPLE 86

4-(2-oxo-5-phenyl-3-benzoxazolinyl)-piperidine

From the reaction of 2-amino-4-phenylphenol and N-t-butyloxycarbonyl-4-piperidone according to Example 15 Steps 2-4 was obtained a white solid.

EXAMPLE 87

4-(6-methoxy-2-oxo-3-benzoxazolinyl)-piperidine

From the reaction of 2-amino-5-methoxyphenol and N-t-butyloxycarbonyl-4-piperidone according to Example 15 Steps 2-4 was obtained a white solid.

EXAMPLE 88

4-(6-carbomethoxy-2-oxo-3-benzoxazolinyl)-piperidine

From the reaction of methyl 4-amino-3-hydroxybenzoate and N-t-butyloxycarbonyl-4-piperidone according to Example 15 Steps 2-4 was obtained a white solid.

EXAMPLE 89

4-(5-ethylsulfonyl-2-oxo-3-benzoxazolinyl)-piperidine

From the reaction of 2-amino-4-(ethylsulfonyl)phenol and N-t-butyloxycarbonyl-4-piperidone according to Example 15 Steps 2-4 was obtained a white solid.

EXAMPLE 90

4-(2-oxo-3-oxazolo[4,5-b]pyridyl)-piperidine

From the reaction of 2-amino-3-hydroxypyridine and N-t-butyloxycarbonyl-4-piperidone according to Example 15 Steps 2-4 was obtained a white solid.

EXAMPLE 91

4-(7-carbethoxy-2-oxo-3-benzoxazolinyl)-piperidine

From the reaction of methyl 3-amino-2-hydroxybenzoate and N-t-butyloxycarbonyl-4-piperidone according to Example 15 Steps 2-4 was obtained a white solid.

EXAMPLE 92

4-(5-tert-butyl-2-oxo-3-benzoxazolinyl)-piperidine

From the reaction of 2-amino-4-tert-butylphenol and N-t-butyloxycarbonyl-4-piperidone according to Example 15 Steps 2-4 was obtained a white solid.

EXAMPLE 93

4-(5,7-dimethyl-2-oxo-3-benzoxazolinyl)-piperidine

From the reaction of 6-amino-2,4-dimethylphenol and N-t-butyloxycarbonyl-4-piperidone according to Example 15 Steps 2-4 was obtained a white solid.

EXAMPLE 94

1,1-Dioxido-2-(4-(4-(1,3-dihydro-2-oxo-2H-benzimidazolin-1-yl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one

From 1,3-dihydro-1-(4-piperidinyl)-2H-benzimidazol-2-one and 2-(4-bromobutyl)-1,1-dioxido-1,2-benzothiazol-3(2H)-one using the procedure described for Example 15, Step 5 there was obtained a white solid: mp 193-5°C; Analysis calculated for $C_{23}H_{26}N_4O_4S$ • 0.5 $CHCl_3$ C: 54.89 H: 5.19, N: 10.90 found C: 54.60, H: 5.24, N: 10.84. ^1H NMR (300 MHz, $CDCl_3$) 10.0 (s, 1H), 8.2 (d, 1H), 8.1-7.9 (m, 3H), 7.4 (dd, 1H), 7.25 (m, 1H), 7.18 (m, 3H), 4.5 (m, 1H), 3.95 (t, 2H), 3.2 (d, J = 12 Hz, 2H), 2.6 (m, 4H), 2.3 (t, J = 12 Hz, 2H), 2.1 (m, 4H), 1.95 (m, 2H), 1.8(m, 2H).

EXAMPLE 95

1,1-Dioxido-2-(4-(4-(1,3-dihydro-2-oxo-3-methyl-2H-benzimidazolin-1-yl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one

Step 1: A mixture of 1 g of 1,3-dihydro-1-(4-piperidinyl)-2H-benzimidazol-2-one, 25 mL of tetrahydrofuran, 10 mL of saturated Na_2CO_3, 20 mL of water and 1.05 g of di-tert-butyl-dicarbonate was stirred for 6 h. The mixture was extracted with 100 mL of chloroform and the organic extracts concentrated to dryness under reduced pressure. Drying under vacuum gave 1.6 g of 1,3-dihydro-1-(1-tert-butyloxycarbonylpiperidin-4-yl)-2H-benzimidazol-2-one as a white crystalline solid.

Step 2: A mixture of 0.060 g of sodium hydride, 60% oil dispersion, 10 mL of DMF, 0.086 mL of iodomethane, and 0.4 g of 1,3-dihydro-1-(1-tert-butyloxycarbonylpiperidin-4-yl)-2H-benzimidazol-2-one was stirred for 12 h, then partitioned between 100 mL of chloroform and 50 mL of water. The chloroform extracts dried over $MgSO_4$, and concentrated under reduced pressure. Trituration with hexane gave 0.38 g of 1,3-dihydro-1-(1-tert-butyloxycarbonylpiperidin-4-yl)-3-

methyl-2H-benzimidazol-2-one as a crystalline solid: ^{1}H NMR (300 MHz, $CDCl_3$) 7.13-7.03 (m, 3H), 6.98 (d, 1H), 4.5 (m, 1H), 4.3 (br m, 2H), 3.4 (s, 3H), 2.85 (m, 4H), 2.3 (m, 2H), 1.8 (d, 2H), 1.5 (s, 9H).

Step 3: A stream of hydrogen chloride gas was dispersed through a stirred, ice cold solution of 0.383 g of 1,3-dihydro-1-(1-tert-butyloxycarbonylpiperidin-4-yl)-3-methyl-2H-benzimidazol-2-one in 500 mL of ethyl acetate for 30 min. Stirring was continued at 0°C for 1 h, then at ambient temperature for 1 h. The suspension was partitioned between 250 mL of chloroform and 50 mL of saturated Na_2CO_3. Drying under reduced pressure gave 0.296 of 1,3-dihydro-1-(4-piperidinyl)-2H-benzimidazol-2-one as an off-white solid.

Step 4: From 1,3-dihydro-1-(4-piperidinyl)-3-methyl-2H-benzimidazol-2-one and 2-(4-bromobutyl)-1,1-dioxido-1,2-benzothiazol-3(2H)-one using the procedure described for Example 15, Step 5 there was obtained a white solid: mp 161-163°C. Analysis calculated for $C_{24}H_{28}N_4O_4S$ C: 61.52, H: 6.02, N: 11.96 found C: 61.44, H: 6.06, N: 11.84. ^{1}H NMR (300 MHz, $CDCl_3$) 8.2 (d, 1H), 8.1-7.9 (m, 3H), 7.13-7.03 (m, 3H), 6.98 (d, 1H), 4.5 (m, 1H), 3.95 (t, 2H), 3.4 (s, 3H), 3.2 (d, J = 12 Hz, 2H), 2.6 (m, 4H), 2.3 (t, J = 12 Hz, 2H), 2.1 (m, 4H), 1.95 (m, 2H), 1.8(m, 2H).

EXAMPLE 96

1,1-Dioxido-2-(4-(4-(1,3-dihydro-2-oxo-5-methyl-2H-benzimidazolin-1-yl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one

Step 1: A mixture of 69 g of 4-chloro-3-nitro-toluene, 50 g of ethyl 4-amino-1-piperidinecarboxylate, 24 g of sodium carbonate, 0.1 g of sodium iodide and 120 mL of cyclohexanol was heated to 150°C for 72 h. After cooling the cyclohexanol was distilled off under reduced pressure and the residue partitioned between 1 L of ethyl acetate and 1 L of water. The organic extract was dried over $MgSO_4$ and concentrated under reduced pressure. Chromatography over silica gel,

eluting with 20% ethyl acetate in cyclohexane gave 38.5 g (42.3%) of ethyl 4-(4-methyl-2-nitroanilino)-1-piperidinecarboxylate as an orange crystalline solid. ^{1}H NMR (400 MHz, $CDCl_3$) 8.0 (s, 1H), 7.27 (t, J = 9 Hz, 1H), 6.8 (d, J = 9 Hz, 1H), 4.15 (q, J = 7 Hz, 2H), 4.05 (br m, 2H), 3.67 (br m, 1H), 3.10 (br t, J = 11 Hz, 2H), 2.27 (s, 3H), 2.06 (br d, J = 11 Hz, 2H), 1.6 (m, 2H), 1.27 (t, J = 7 Hz, 4H).

Step 2: A mixture of 8.23 g of ethyl 4-(4-methyl-2-nitroanilino)-1-piperidinecarboxylate, 200 mL of tetrahydrofuran , 225 mL of ethanol and 2 g of 5% platinum on carbon was stirred under an atmosphere of hydrogen for 7 h. The catalyst was filtered off and the filtrate concentrated to to a thick oil. To an ice cold, vigorously stirred solution of the resulting crude ethyl 4-(4-methyl-2-aminoanilino)-1-piperidinecarboxylate in 500 mL of ethyl acetate was added 500 mL of saturated sodium carbonate followed by 20 mL of 1.9 M phosgene in toluene dropwise over 30 min. After stirring overnight at room temperature, the layers were separated and the organic layer dried over $MgSO_4$ and concentrated to dryness. Trituration of the residue with ether-hexane gave 8 g of ethyl 4-(5-methyl-2-oxo-1-benzimidazolinyl)piperidine-1-carboxylate as a white crystalline solid.

Step 3: A mixture of 5 g of ethyl 4-(5-methyl-2-oxo-1-benzimidazolinyl)piperidine-1-carboxylate and 20 mL of 2N NaOH was heated under reflux for 12 h. The resulting solution is cooled and stirred for for 30 minutes with 5 g of ammonium chloride and extracted with three 200 mL portions of chloroform. The combined organic extracts were dried over $MgSO_4$, concentrated under reduced pressure and triturated with ether. The solid product 1,3-dihydro-1-(4-piperidinyl)-5-methyl-2H-benzimidazol-2-one weighed 3.5 g after drying.

Step 4: From 1,3-dihydro-1-(4-piperidinyl)-5-methyl-2H-benzimidazol-2-one and 2-(4-bromobutyl)-1,1-dioxido-1,2-benzothiazol-3(2H)-one using the procedure described for Example 15, Step 5 there was obtained a white solid: mp 104-6°C; Analysis calculated for $C_{24}H_{28}N_4O_4S \cdot 0.35\ CH_3OH \cdot 0.35\ CH_2Cl_2$ C: 58.22, H: 5.95, N: 11.00 found C: 58.43, H: 5.91, N: 10.60.

EXAMPLE 97

1,1-Dioxido-2-(4-(4-(1,3-dihydro-2-oxo-4-methyl-2H-benzimidazolin-1-yl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one

From 1,3-dihydro-1-(4-piperidinyl)-4-methyl-2H-benzimidazol-2-one and 2-(4-bromobutyl)-1,1-dioxido-1,2-benzothiazol-3(2H)-one using the procedure described for Example 15, Step 5 there was obtained a white solid: mp 90-2°C; Analysis calculated for $C_{24}H_{28}N_4O_4S$•0.5 CH_2Cl_2 C: 57.58, H: 5.72, N: 10.96 found C: 57.41, H: 5.74, N: 10.96.

EXAMPLE 98

1,1-Dioxido-2-(4-(4-(1,3-dihydro-2-oxo-5-methoxy-2H-benzimidazolin-1-yl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one

From 4-chloro-3-nitro-anisole using the procedures described for Example 96, Steps 1 through 4, there was obtained a white solid: mp 162-4°C; Analysis calculated for $C_{24}H_{28}N_4O_5S$•0.5 CH_3OH C: 58.78, H: 6.04, N: 11.19 found C: 58.99, H: 5.88, N: 10.87.

EXAMPLE 99

1,1-Dioxido-2-(4-(4-(1,3-dihydro-2-oxo-5-chloro-2H-benzimidazolin-1-yl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one

From 2,5-dichloronitrobenzene using the procedures described for Example 96, Steps 1 through 4, there was obtained a white solid: mp 206-8°C; Analysis calculated for $C_{23}H_{25}ClN_4O_4S$•0.8 CH_2Cl_2 C: 54.46, H: 5.11, N: 10.68 found C: 54.34, H: 4.87, N: 10.81.

EXAMPLE 100

1,1-Dioxido-2-(4-(4-(1,3-dihydro-2-oxo-5-fluoro-2H-benzimidazolin-1-yl)-piperidin-1-yl)-butyl)-5-chloro-1,2-benzisothiazol-3(2H)-one

From 2-chloro-5-fluoronitrobenzene using the procedures described for Example 96, Steps 1 through 4, and 2-(4-bromobutyl)-1,1-dioxido-5-chloro-1,2-benzisothiazol-3(2H)-one there was obtained a white solid: mp 259-61°C; Analysis calculated for $C_{23}H_{24}FClN_4O_4S \cdot HCl$ C: 50.83, H: 4.64, N: 10.31 found C: 50.74, H: 4.60, N: 10.18.

EXAMPLE 101

1,1-Dioxido-2-(4-(4-(1,3-dihydro-2-oxo-5-methyl-2H-benzimidazolin-1-yl)-piperidin-1-yl)-butyl)-5-chloro-1,2-benzisothiazol-3(2H)-one

From 1,3-dihydro-1-(4-piperidinyl)-5-methyl-2H-benzimidazol-2-one and 2-(4-bromobutyl)-1,1-dioxido-5-chloro-1,2-benzisothiazol-3(2H)-one using the procedure described for Example 15, Step 5 there was obtained a white solid: mp 258-60°C; Analysis calculated for $C_{23}H_{27}ClN_4O_4S \cdot HCl \cdot 0.4\ H_2O$ C: 52.72, H: 5.31, N: 10.25 found C: 52.75, H: 5.23, N: 10.25.

EXAMPLE 102

1,1-Dioxido-2-(4-(4-(1,3-dihydro-2-oxo-6-methyl-2H-benzimidazolin-1-yl)-piperidin-1-yl)-butyl)-5-chloro-1,2-benzisothiazol-3(2H)-one

From 1,3-dihydro-1-(4-piperidinyl)-5-methyl-2H-benzimidazol-2-one and 2-(4-bromobutyl)-1,1-dioxido-5-chloro-1,2-benzisothiazol-3(2H)-one using the procedure described for Example 15, Step 5 there was obtained a white solid: mp 273-75°C; Analysis calculated for $C_{23}H_{27}ClN_4O_4S \cdot HCl \cdot 0.5\ H_2O$ C: 52.55, H: 5.33, N: 10.22 found C: 52.52, H: 5.05, N: 10.16.

EXAMPLE 103

1,1-Dioxido-2-(4-(4-(5-methyl-2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-5,6-dihydro-[1,4]dioxino[2,3-e]benzisothiazol-3(2H)-one

From 4-(5-methyl-2-oxo-3-benzoxazolinyl)-piperidine and 2-(4-hydroxybutyl)-1,1-dioxido-5,6-dihydro-[1,4]dioxino[2,3-d]benzisothiazol-3(2H)-one using the procedure described for Example 66, Steps 4-6 there was obtained a white solid: mp 98-101 °C Analysis calculated for $C_{26}H_{29}N_3O_7S \bullet 0.3\ CHCl_3$ C: 56.06, H: 5.24, N: 7.46 found C: 56.11, H: 5.30, N: 7.45. ^1H NMR (300 MHz, $CDCl_3$) 7.4 (d, H), 7.27 (d, 1H), 7.18 (d, 1H), 7.05 (s, 1H), 6.95 (d, 1H), 4.5 (m, 2H), 4.4 (m, 2H), 4.2 (m, 1H), 3.8 (t, 2H), 3.08 (d, 2H), 2.44 (t, 2H), 2.39 (s, 3H), 2.1 (t, 2H), 1.85 (m, 4H), 1.71 (m, 2H), 1.65 (m, 2H).

EXAMPLE 104

1,1-Dioxido-2-(4-(4-(2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-5,6-dihydro-[1,4]dioxino[2,3-e]benzisothiazol-3(2H)-one

From 4-(2-oxo-3-benzoxazolinyl)-piperidine and 2-(4-hydroxybutyl)-1,1-dioxido-5,6-dihydro-[1,4]dioxino[2,3-d]benzisothiazol-3(2H)-one using the procedure described for Example 66, Steps 4-6 there was obtained a white solid: mp 79-82 °C ^{1}H NMR (400 MHz, $CDCl_3$) 7.4 (d, 1H), 7.3 (m, 2H), 7.2-7.0 (br m, 3H), 4.5 (m, 2H), 4.4 (m, 2H), 4.2 (m, 1H), 3.8 (m, 2H), 3.1 (br d, 2H), 2.5-2.4 (br m, 2H), 2.2 (m, 2H), 2.0-1.85 (br m, 4H), 1.80 (m, 2H), 1.7 (m, 2H) Analysis calculated for $C_{25}H_{27}N_3O_7S \cdot 0.3\ CHCl_3$ C: 55.31, H: 5.01, N: 7.65 found C: 55.20, H: 5.08, N: 7.39.

EXAMPLE 105

1,1-Dioxido-2-(4-(4-(spiro-1,3-dihydro-1-oxo-2H-indenyl)-2,4'-piperidin-1'-yl)-butyl)-5,6-dihydro-[1,4]dioxino[2,3-e]benzisothiazol-3(2H)-one

From 1,3-dihydro-1-oxo-spiro(2H-indenyl-2,4'-piperidine) and 2-(4-hydroxybutyl)-1,1-dioxido-5,6-dihydro-[1,4]dioxino[2,3-d]benzisothiazol-3(2H)-one using the procedure described for Example 66, Steps 4-6 there was obtained a white solid: Analysis calculated for $C_{26}H_{298}N_2O_6S \cdot 0.4\ CHCl_3$ C: 58.25, H: 5.26, N: 5.15 found C: 58.36, H: 5.40, N: 5.20.

EXAMPLE 106

1,1-Dioxido-2-(4-(4-(1,3-dihydro-2-oxo-1H-3,4-dihydroquinazolin-1-yl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one

Step 1: A mixture of 45 g of 2-aminomethylaniline, 60 g of di-*tert* -butyldicarbonate, 1000 mL of dichloromethane was stirred for 18 h and washed with 500 mL of 2N NaOH. The organic extract was dried

over $MgSO_4$ and concentrated under reduced pressure. Drying under vacuum gave 47 g of 2-(*tert* -butoxycarbonylaminomethyl)aniline as a white crystalline solid. ^1H NMR (400 MHz, $CDCl_3$) 7.1 (t, 1H), 7.05 (d, 1H), 6.65 (dd, 2H), 4.8 (br s, 1H), 4.2 (br m, 4H), 1.44 (s, 9H).

Step 2: A mixture of 15.5 g of 2-(*tert* -butoxycarbonyl aminomethyl)aniline, 15 g of N-t-butyloxycarbonyl-4-piperidone, 250 mL of 1,2-dichloroethane, 4.2 mL of glacial acetic acid and 25 g of sodium triacetoxyborohydride was stirred at room temperature for 48 h. The reaction mixture was poured into 500 mL chloroform and 500 mL saturated aqueous Na_2CO_3 and the layers separated. The aqueous layer was extracted with 2 X 250 mL of chloroform and the combined organic layers dried over $MgSO_4$ and concentrated under reduced pressure. Drying overnight under vacuum gave 30.1 g of *tert* -butyl (2-(*tert* -butoxycarbonyl aminomethyl)anilino)piperidine carboxylate as a solid: ^1H NMR (400 MHz, $CDCl_3$) 7.19 (t, 1H), 7.0 (d, 1H), 6.6 (dd, 2H), 4.94 (br s, 1H), 4.75 (br s, 1H), 4.23 (br m, 2H), 4.0 (br m, 2H), 3.45 (br m, 1H), 3.0 (br m, 2H), 2.0 (br m, 2H), 1.82 (br m, 1H), 1.46 (s, 9H), 1.44 (s, 9H).

Step 3: To a stirred solution of 27.1 g of *tert* -butyl 4-(2-*tert* -butoxycarbonylaminomethylanilino)-1-piperidinecarboxylate and 30 mL of triethylamine in 400 mL of dichloromethane was added dropwise 60 mL of a 1.93 M solution of phosgene in toluene. After stirring for 12 h, 200 mL of 1N NaOH was added. The mixture was shaken, and the organic layer separated, dried over $MgSO_4$ and concentrated under reduced pressure. Chromatography on silica gel, eluting with 25% ethyl acetate in hexane gave, after drying overnight under vacuum, 25 g of 1,3-dihydro-1-[1-*tert* -butoxycarbonylpiperidin-4-yl]-3-*tert* -butoxycarbonyl-1H-3,4-dihydroquinazolin-2-one carboxylate as a clear glass: ^1H NMR (400 MHz, $CDCl_3$) 7.52 (d, 1H), 7.45 (t, 1H), 7.36 (m, 1H), 7.10 (d, 1H), 4.2-4.0 (br m, 5H), 3.65-3.25 (br m, 2H), 2.75 (br m, 2H), 2.28 (br d, 1H), 1.8 (br d, 1H), 1.5 (s, 9H), 1.49 (s, 9H).

Step 4: A stirred solution of 25 g of 1,3-dihydro-1-[1-*tert* -butoxycarbonylpiperidin-4-yl]-3-*tert* -butoxycarbonyl-1H-3,4-dihydroquinazolin-2-one carboxylate in 1 L of ethyl acetate cooled to

-50°C was saturated with hydrogen chloride gas for 15 min. The resulting mixture was allowed to warm to room temperature and stir for 4 h. The white solid precipitate was collected by filtration. Drying under vacuum gave 13.1 of 1,3-dihydro-1-[piperidin-4-yl]-3-*tert* -butoxycarbonyl-1H-3,4-dihydroquinazolin-2-one hydrochloride salt as a white solid. The salt (0.8 g) was converted to the free base by partitioning between chloroform and saturated sodium carbonate. Drying under vacuum gave 0.68 g of 1,3-dihydro-1-[piperidin-4-yl]-1H-3,4-dihydroquinazolin-2-one as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) 7.25 (dd, 1H), 7.12 (d, 1H), 7.06 (d, 1H), 6.98 (t, 1H), 5.2 (br s, 1H), 4.28 (s, 2H), 4.10 (m, 1H), 3.22 (d, 2H), 2.73 (m, 2H), 2.59 (m, 2H), 2.05 (br s, 1H), 1.82 (br d, 2H).

Step 5: From 1,3-dihydro-1-[piperidin-4-yl]-1H-3,4-dihydroquinazolin-2-one and 2-(4-bromobutyl)-1,1-dioxido-1,2-benzothiazol-3(2H)-one using the procedure described for Example 15, Step 5 there was obtained a white solid: Analysis calculated for $C_{24}H_{28}N_4O_4S \cdot 0.35\ CHCl_3 \cdot 0.45\ H_2O$ C: 52.70 H: 5.49, N: 10.10 found C: 52.71, H: 5.49, N: 10.33.

EXAMPLE 107

2-(4-Hydroxybutyl)-1,1-dioxido-5,6-dihydro-[1,4]dioxino[2,3-d]benzisothiazol-3(2H)-one

Step 1: To a stirred solution of 12 g of 1,4-benzodioxane in 40 mL of chloroform cooled to -10C under calcium sulfate drying tube was added dropwise over 15 min, 6 mL of chlorosulfonic acid. The mixture was allowed to warm to 20C over 15 min, poured onto 400 mL of ice and extracted into 1 L of chloroform. Drying over $MgSO_4$ and concentration under reduced pressure gave 21.5 g of 1,4-benzodioxane-6-sulfonylchloride as a white crystalline solid.

Step 2: To an ice cold, stirred solution of 10 g of 4-aminobutanol and 25 mL of triethylamine in 250 mL of dichloromethane was added a solution of 21.5 g of 1,4-benzodioxane-6-sulfonylchloride in 100 mL of chloroform over 30 min. The mixture was allowed to warm and stir overnight, washed with 100 mL of 6N HCl and dried over $MgSO_4$. To

this solution was added 300 mL of dichloromethane, 20 mL of dihydropyran and 100 mg of p-toluenesulfonic acid monohydrate. After stirring for 12 h, the mixture was washed with 100 mL of saturated Na_2CO_3, dried over $MgSO_4$ and concentrated under reduced pressure. Chromatography on silica gel, eluting with 30% ethyl acetate in hexane gave, after drying overnight under vacuum, 13 g of N-(4-(2-tetrahydropyranyloxy)butyl)-1,4-benzodioxane-6-sulfonamide as a resin.

Step 3: To a stirred solution of 13 g of N-(4-(2-tetrahydropyranyloxy)butyl)-1,4-benzodioxane-6-sulfonamide in 250 mL of dry tetrahydrofuran cooled to -78^{o}C was added 50 mL of commercial 1.6M n-butyllithium in hexane over 10 min. After aging for 60 min with warming to 0^{o}C, the solution was cooled to -78^{o}C and quenched by a stream of carbon dioxide gas with a fritted glass dispersion tube, keepiing the temperature below -40^{o}C for 30 min. The solution was allowed to warm to room temprature over 1 h and partitioned between 200 mL of water, 200 mL of saturated Na_2CO_3 and3 x 200 mL of ether. The aqueous layer was carefully acidified to pH=3 with concentrated HCl, and extracted with 3 x 200 mL portions of ether. The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. Drying under vacuum gave 10.1 g of N-(4-(2-tetrahydropyranyloxy)butyl) 5-carboxy-1,4-benzodioxane-6-sulfonamide as a foam.

Step 4: To a stirred solution of 10 g of N-(4-(2-tetrahydropyranyloxy)butyl) 5-carboxy-1,4-benzodioxane-6-sulfonamide and 7 mL of triethylamine in 200 mL of dichloromethane cooled to 0^{o}C was added 2 mL of methyl chloroformate dropwise. After 3 h at 20°C, the mixture was shaken with 50 mL of saturated sodium carbonate, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was disolved in 200 mL of methanol containing 1 g of p-toluenesulfonic acid monohydrate, stirred overnight at ambient temperature, and concentrated to dryness under reduced pressure. The residue was dissolved in 200 mL of ethyl acetate, washed with 5 mL of saturated sodium carbonate, dried over $MgSO_4$

and concentrated under reduced pressure. Trituration with ether gave 4 g of 2-(4-hydroxybutyl)-1,1-dioxido-5,6-dihydro-[1,4]dioxino[2,3-d]benzisothiazol-3(2H)-one as a white crystalline solid: mp °C; ^1H NMR (400 MHz, $CDCl_3$): 7.4 (d, 1H), 7.25 (d, 1H), 4.5 (m, 2H), 4.4 (m, 2H), 3.8 (t, 2H), 3.7 (t, 2H), 1.95 (m, 2H), 1.7 (m, 2H), 1.55 (br s, 1H).

EXAMPLE 108

2-(4-Hydroxybutyl)-1,1-dioxido-5-ethoxy-1,2-benzothiazol-3(2H)-one

From ethoxybenzene using the procedures described for Example 107, Steps 1-4 there was obtained a thick oil.

EXAMPLE 109

2-(4-Hydroxybutyl)-1,1-dioxido-5-ethyl-1,2-benzothiazol-3(2H)-one

From 4-ethylbenzenesulfonylchloride using the procedures described for Example 107, Steps 2-4 there was obtained a thick oil.

EXAMPLE 110

2-(4-Hydroxybutyl)-1,1-dioxido-5-isopropyl-1,2-benzothiazol-3(2H)-one

From 4-isopropylbenzenesulfonylchloride using the procedures described for Example 107, Steps 2-4 there was obtained a thick oil.

EXAMPLE 111

1,1-Dioxido-2-(4-(4-(2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-5-ethoxy-1,2-benzothiazol-3(2H)-one

From 4-(2-oxo-3-benzoxazolinyl)-piperidine and 2-(4-hydroxybutyl)-1,1-dioxido-5-ethoxy-1,2-benzothiazol-3(2H)-one using the procedure

described for Example 66, Steps 4-6 there was obtained a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) 7.79 (d, J = 8.57 Hz, 1H), 7.44 (s, 1H), 7.29-7.26 (m, 2H), 7.21 (d, J = 6.89 Hz, 1H), 7.16-7.06 (m, 2H), 4.24-4.11 (m, 1H), 3.81 (t, J = 7.3 Hz, 2H), 3.06 (br d, J = 11.76 Hz, 2H), 2.45 (t, J = 7.39 Hz, 2H), 2.36 (m, 2H), 2.11 (bt, J = 11.08 Hz, 2H), 1.93-1.80 (br m, 6H), 1.65 (br m, 2H), 1.48 (t, J = 6.97, 3H) Analysis calculated for $C_{25}H_{30}N_3O_6S$ • HCl • 1.2 H_2O C: 53.75, H: 6.03, N: 7.52 found C: 53.72, H: 5.65 N: 7.52.

EXAMPLE 112

1,1-Dioxido-2-(4-(4-(spiro-1,3-dihydro-1-oxo-2H-indenyl)-2,4'-piperidin-1'-yl)-butyl)-5-ethoxy-1,2-benzothiazol-3(2H)-one

From 1,3-dihydro-1-oxo-spiro(2H-indenyl-2,4'-piperidine) and 2-(4-hydroxybutyl)-1,1-dioxido-5-ethoxy-1,2-benzothiazol-3(2H)-one using the procedure described for Example 66, Steps 4-6 there was obtained a white solid: Analysis calculated for $C_{26}H_{30}N_2O_5S$ • HCl • 0.45 H_2O • 0.3 $CHCl_3$ C: 56.11, H: 5.77, N: 4.98 found C: 56.14, H: 5.74, N: 5.18.

EXAMPLE 113

1,1-Dioxido-2-(4-(4-(spiro-1,3-dihydro-1-oxo-2H-indenyl)-2,4'-piperidin-1'-yl)-butyl)-5-ethyl-1,2-benzothiazol-3(2H)-one

From 1,3-dihydro-1-oxo-spiro(2H-indenyl-2,4'-piperidine) and 2-(4-hydroxybutyl)-1,1-dioxido-5-ethyl-1,2-benzothiazol-3(2H)-one using the procedure described for Example 66, Steps 4-6 there was obtained a white solid: Analysis calculated for $C_{26}H_{30}N_2O_4S$ • HCl • 0.2 $CHCl_3$ C: 59.71, H: 5.97, N: 5.32 found C: 59.66, H: 6.16, N: 5.35.

EXAMPLE 114

1,1-Dioxido-2-(4-(4-(2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-5-ethyl-1,2-benzothiazol-3(2H)-one

From 4-(2-oxo-3-benzoxazolinyl)-piperidine and 2-(4-hydroxybutyl)-1,1-dioxido-5-ethyl-1,2-benzothiazol-3(2H)-one using the procedure described for Example 66, Steps 4-6 there was obtained a white solid: mp 165-168 °C ^{1}H NMR (400 MHz, $CDCl_3$) 7.9 (s, 1H), 7.8 (m, 1H), 7.66 (m, 1H), 7.3 (m, 1H), 7.2-7.05 (m, 3H), 4.2 (m, 1H), 3.8 (m, 2H), 3.1 (m, 2H), 2.82 (m, 2H), 2.4 (m, 2H), 2.1 (m, 2H), 2.0-1.8 (br m, 4H), 1.8-1.6 (br m, 4H), 1.3 (t, 3H) Analysis calculated for $C_{25}H_{30}N_3O_6S$ • HCl • 1.4 H_2O C: 55.66, H: 6.06, N: 7.01 found C: 55.82, H: 5.81, N: 6.91.

EXAMPLE 115

1,1-Dioxido-2-(4-(4-(spiro-1,3-dihydro-1-oxo-2H-indenyl)-2,4'-piperidin-1'-yl)-butyl)-5-(2-propyl)-1,2-benzothiazol-3(2H)-one

From 1,3-dihydro-1-oxo-spiro(2H-indenyl-2,4'-piperidine) and 2-(4-hydroxybutyl)-1,1-dioxido-5-(2-propyl)-1,2-benzothiazol-3(2H)-one using the procedure described for Example 66, Steps 4-6 there was obtained a white solid: Analysis calculated for $C_{27}H_{32}N_2O_4S$ • HCl • 1.00 H_2O C: 60.60, H: 6.59, N: 5.24 found C: 60.62, H: 6.36, N: 5.28.

EXAMPLE 116

1,1-Dioxido-2-(4-(4-(2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-5-(2-propyl)-1,2-benzothiazol-3(2H)-one

From 4-(2-oxo-3-benzoxazolinyl)-piperidine and 2-(4-hydroxybutyl)-1,1-dioxido-5-(2-propyl)-1,2-benzothiazol-3(2H)-one using the procedure described for Example 66, Steps 4-6 there was obtained a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) 7.9 (s, 1H), 7.8 (d, 1H), 7.7 (d, 1H), 7.3 (m, 1H), 7.2-7.0 (br m, 3H), 4.2 (m, 1H), 3.8 (m, 2H),

3.1 (m, 3H), 2.7-2.5 (br m, 2H), 2.1 (m, 2H), 2.0 - 1.8 (br m, 4H), 1.7-1.6 (m, 4H), 1.35 (d, 6H) Analysis calculated for $C_{25}H_{30}N_3O_6S$ • HCl • 1.6 $CH_3CO_2CH_2CH_3$ C: 57.64, H: 6.69, N: 6.23 found C: 57.06, H: 6.12, N: 6.56.

The following Examples 117-144 were made in the same manner as described in detail above using readily available starting materials.

EXAMPLE 117

1,1-Dioxido-2-(4-(4-(2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-6-nitro-1,2-benzisothiazol-3(2H)-one

^{1}H NMR (400 MHz, $CDCl_3$) 8.78 (d, J = 1.46 Hz, 1H), 8.70 (dd, J = 8.39 Hz, 2.01 Hz, 1H), 8.29 (dd, J = 8.39 Hz, 0.4 Hz, 1H), 7.26-7.08 (m, 4H), 4.21 (dt, J = 12.43 Hz, 4.2 Hz, 1H), 3.91 (t, J = 7.40 Hz, 2H), 3.08 (d, J = 11.58 Hz, 2H), 2.47 (t, J = 7.22 Hz, 2H), 2.39 (dq, J = 12.43 Hz, 3.80 Hz, 2H), 2.12 (t, J = 10.24 Hz, 2H), 1.95 (q, J = 7.56 Hz, 2H), 1.87 (dd, J = 11.92 Hz, 2.01 Hz, 2H), 1.65 (q, J = 7.89 Hz, 2H).

EXAMPLE 118

1,1-Dioxido-2-(4-(4-(2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-5-fluoro-1,2-benzisothiazol-3(2H)-one

^{1}H NMR (400 MHz, $CDCl_3$) 7.95 (dd, J = 4.37 Hz, 4.20 Hz, 1H), 7.73 (dd, J = 7.05 Hz, 2.35 Hz, 1H), 7.56 (dt, J = 8.39 Hz, 2.52 Hz, 1H), 7.25 (s, 1H), 7.20 (d, J = 7.89 Hz, 1H), 7.14 (dt, J = 7.55 Hz, 1.18 Hz, 1H), 7.09 (dq, J = 7.72 Hz, 1.18 Hz, 1H), 4.22 (tt, J = 12.42 Hz, 4.2 Hz, 1H), 3.84 (t, J = 7.39 Hz, 2H), 3.07 (d, J = 11.75 Hz, 2H), 2.45 (t, J = 7.22 Hz, 2H), 2.38 (dq, J = 8.70 Hz, 3.90 Hz, 2H), 2.12 (dt, J = 11.75 Hz, 1.51 Hz, 2H), 1.82 - 1.60 (m, 4H), 1.64 (q, J = 7.56 Hz, 2H).

EXAMPLE 119

1,1-Dioxido-2-(4-(4-(2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-5-methyl-1,2-benzisothiazol-3(2H)-one

^{1}H NMR (400 MHz, $CDCl_3$) 7.86 (s, 1H), 7.81 (d, J = 7.89 Hz, 1H), 7.66 (d, J = 8.06 Hz, 1H), 7.21 (d, J = 7.55 Hz, 1H), 7.15 (t, J = 6.21 Hz, 1.51 Hz, 1H), 4.2 (m, 1H), 3.83 (t, J = 7.39 Hz, 2H), 3.08 (d, J = 11.75 Hz, 2H), 2.56 (s, 3H), 2.45 (t, J = 6.88 Hz, 2H), 2.37 (dt, J = 8.22 Hz, 3.86 Hz, 2H), 2.11 (t, J = 12.26 Hz, 2H), 1.94 - 1.85 (m, 4H), 1.63 (m, 2H).

EXAMPLE 120

1,1-Dioxido-2-(4-(4-(2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-5-bromo-1,2-benzisothiazol-3(2H)-one

mp 158-162 °C ^{1}H NMR (400 MHz, $CDCl_3$) 8.20 (m, 1H), 7.99 (dd, 1H), 7.79 (d, 1H), 7.22 - 7.06 (m, 4H), 4.21 (m, 1H), 3.83 (t, 2H), 3.07 (d, 2H), 2.55 (t, 2H), 2.42-2.30 (m, 2H), 2.10 (t, 2H), 1.94-1.82 (m, 4H), 1.61 (m, 2H).

EXAMPLE 121

1,1-Dioxido-2-(4-(4-(2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-5-trifluoromethyl-1,2-benzisothiazol-3(2H)-one

mp 177-179 °C ^{1}H NMR (400 MHz, $CDCl_3$) 8.38 (s, 1H), 8.18 (d, 1H), 8.10 (d, 1H), 7.25 (m, 1H), 7.2 (d, 1H), 7.1-7.2 (m, 2H), 4.2 (m, 1H), 3.88 (m, 2H), 3.05 (br d, 2H), 2.45 (m, 2H), 2.4 (m, 2H), 2.1 (m, 2H), 1.82-2.0 (br m, 4H), 1.75-1.6 (m, 2H).

EXAMPLE 122

1,1-Dioxido-2-(4-(4-(2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-5-trifluoromethoxy-1,2-benzisothiazol-3(2H)-one

mp 230-233 °C ^{1}H NMR (400 MHz, $CDCl_3$) 8.0 (d, 1H), 7.9 (s, 1H), 7.68 (d, 1H), 7.25 (d, 1H), 7.20 (d, 1H), 7.1-7.19 (m, 2H), 4.2 (m, 1H), 3.83 (m, 2H), 3.05 (br d, 2H), 2.42 (m, 2H), 2.4 (m, 2H), 2.1 (m, 2H), 2.8-1.8 (br m, 4H), 1.6 (m, 2H).

EXAMPLE 123

1,1-Dioxido-2-(4-(4-(2-oxo-1-naphth[1,2-d]oxazolinyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one

^{1}H NMR (400 MHz, CD_3OD) 7.46 (d, J = 8.61 Hz, 1H), 7.24 (dd, J = 6.77, 0.73 Hz, 1H), 7.21 (d, J = 7.32 Hz, 1H), 7.16-7.09 (m, 3H), 6.90 (d, J = 8.79 Hz, 1H), 6.79 (t, J = 7.30 Hz, 1H), 6.66 (t, J = 7.51 Hz, 1H), 6.64 (d, J = 8.79 Hz, 1H), 4.35 (m, 1H), 3.03 (t, J = 6.22 Hz, 2H), 2.89 (d, J = 12.63 Hz, 2H), 2.63 (q, J = 6.96 Hz, 1H), 2.53 (br t, J = 12.45 Hz, 1H), 2.41 (br m, 2H), 2.17 (br m, 2H), 1.48 (br d, J = 13.55 Hz, 2H), 1.10 (br m, 4H).

EXAMPLE 124

1,1-Dioxido-2-(4-(4-(5,6,7,8-tetrahydro-2-oxo-3-naphth[2,3-d]oxazolinyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one

^{1}H NMR (300 MHz, CD_3OD) 8.09 (m, 2H), 7.98 (m, 2H), 7.08 (s, 1H), 6.93 (s, 1H), 3.87 (m, 2H), 3.74 (d, J = 12.21 Hz, 2H), 3.24 (br m, 4H), 2.79 (br m, 6H), 2.13 (br d, J = 13.54 Hz, 2H), 1.95 (br d, J = 3.47 Hz, 4H), 1.89 (s, 4H).

EXAMPLE 125

1,1-Dioxido-2-(4-(4-(5-methyl-2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one

^{1}H NMR (400 MHz, CDCl3) 8.08 (d, J = 7.05 Hz, 1H), 7.95-7.85 (m, 4H), 7.06 (d, J = 8.23 Hz, 1H), 6.92 (d, J = 8.22 Hz, 1H), 4.58 (br t, J = 11.92 Hz, 1H), 3.86 (t, J = 6.55 Hz, 2H), 3.72 (d, J = 10.58 Hz, 2H), 3.34 (q, J = 11.25 Hz, 2H), 3.13 (br m, 2H), 2.93 (br m, 2H), 2.45 (s, 3H), 2.11 - 1.99 (m, 6H).

EXAMPLE 126

1,1-Dioxido-2-(4-(4-(5-carbomethoxy-2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one

^{1}H NMR (400 MHz, CDCl3) 8.63 (s, 1H), 8.09 (d, J = 7.05 Hz, 1H),7.96-7.86 (m, 5H), 4.61 (br t, J = 13.09 Hz, 1H), 4.00 (s, 3H), 3.87 (t, J = 6.72 Hz, 2H), 3.75 (d, J = 10.91, 2H), 3.41 (q, J = 12.26, 2H), 3.13 (m, 2H), 2.93 (m, 2H), 2.13-2.00 (m, 6H).

EXAMPLE 127

1,1-Dioxido-2-(4-(4-(6-fluoro-2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one

mp 154-155 °C ^{1}H NMR (400 MHz, CDCl3) 8.06 (dd, 1H), 7.96-7.82 (m, 3H), 7.18 (br q, 1H), 6.99 (dd, 1H), 6.88 (td, 1H), 4.19 (m, 1H), 3.84 (t, 2H), 3.06 (d, 2H), 2.44 (t, 2H), 2.40-2.25 (m, 2H), 2.10 (t, 2H), 1.96-1.81 (m, 4H), 1.61 (bs, 2H).

EXAMPLE 128

1,1-Dioxido-2-(4-(4-(4-methyl-2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one

^{1}H NMR (400 MHz, $CDCl_3$) 8.07 (dd, J = 6.72, 1.52 Hz, 1H), 7.93 (d, J = 6.55 Hz, 1H), 7.85 (m, 2H), 7.03 (d, J = 7.05 Hz, 1H), 6.97 (t, J = 7.72 Hz, 1H), 6.89 (d, J = 7.72 Hz, 1H), 4.21 (dt, J = 8.23, 3.86 Hz, 1H), 3.86 (t, J = 7.21 Hz, 2H), 3.09 (d, J = 11.92 Hz, 2H), 2.71 (dq, J = 8.72, 3.7 Hz, 2H), 2.55 (s, 3H), 2.43 (t, J = 7.56 Hz, 2H), 2.03 (t, J = 12.08 Hz, 2H), 1.91 (m, 2H), 1.65 (d, J = 7.72 Hz, 2H), 1.63-1.59 (m, 2H).

EXAMPLE 129

1,1-Dioxido-2-(4-(4-(4-methoxy-2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one

^{1}H NMR (400 MHz, $CDCl_3$) 8.07 (dd, J = 5.37, 1.01 Hz, 1H), 7.94-7.82 (m, 3H), 7.04 (t, J = 8.22 Hz, 1H), 6.85 (dd, J = 7.21, 0.84 Hz, 1H), 6.73 (d, J = 8.56 Hz, 1H), 4.45 (tt, J = 12.25, 4.2 Hz, 1H), 3.94 (s, 3H), 3.84 (t, J = 7.39 Hz, 2H), 3.04 (br d, J = 11.58 Hz, 2H), 2.54 (qd, J = 8.73, 3.69 Hz, 2H), 2.43 (t, J = 7.22, 2H), 2.07 (dt, J = 10.24, 1.68 Hz, 2H), 1.93 (m, 2H), 1.77 (br d, J = 9.74 Hz, 2H), 1.63 (m, 2H).

EXAMPLE 130

5-Chloro-1,1-dioxido-2-(4-(4-(6-methyl-2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one

^{1}H NMR (400 MHz, $CDCl_3$) 8.04 (d, J = 1.68 Hz, 1H), 7.85 (overlapping t and dt, 2H), 7.13 (d, J = 8.05 Hz, 1H), 7.04 (s, 1H), 6.95 (d, J = 8.05 Hz, 1H), 4.19 (dt, J = 12.42, 4.02 Hz, 1H), 3.84 (t, J = 7.39 Hz, 2H), 3.07 (d, J = 11.59 Hz, 2H), 2.45 (t, J = 7.39 Hz, 2H), 2.38 (s, 3H), 2.33 (dq, J = 12.25, 3.52 Hz, 2H), 2.11 (t, J = 11.58 Hz, 2H), 1.95-1.84 (m, 4H), 1.63 (m, 2H).

EXAMPLE 131

5-Methylthio-1,1-dioxido-2-(4-(4-(6-methyl-2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one

^{1}H NMR (400 MHz, $CDCl_3$) 7.78 (t, J = 1.68 Hz, 1H), 7.75 (s, 1H), 7.62 (dd, J= 8.23, 1.85 Hz, 1H), 7.15 (br d, J = 7.39 Hz, 1H), 7.02 (s, 1H), 6.94 (d, J = 8.06 Hz, 1H), 4.19 (m, 1H), 3.82 (t, J = 7.22 Hz, 2H), 3.08 (br d, J = 9.56 Hz, 2H), 2.60 (s, 3H), 2.46 (br m, 2H), 2.37 (s, 3H), 2.42-2.37 (br m, 2H), 2.15-2.11 (br m, 2H), 1.94-1.83 (br m, 4H), 1.66-1.64 (br m, 2H).

EXAMPLE 132

5-Ethoxy-1,1-dioxido-2-(4-(4-(6-methyl-2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one

^{1}H NMR (400 MHz, $CDCl_3$) 7.79 (dd, J = 8.56, 3.53 Hz, 1H), 7.44 (dd, J = 4.36, 2.35 Hz, 1H), 7.29 (m, 1H), 7.14 (d, J = 8.06 Hz, 1H), 7.02 (s, 1H), 6.94 (br d, J = 7.22 Hz, 1H), 4.18 (m, 3H), 3.81 (t, J = 7.38 Hz, 2H), 3.71 (t, J = 6.38 Hz, 1H), 3.06 (d, J = 11.75 Hz, 2H), 2.44 (t, J = 7.38 Hz, 2H), 2.37 (s, 3H), 2.31 (dt, J = 12.26, 3.53 Hz, 1H), 2.10 (dt, J = 11.92, 2.02 Hz, 2H), 1.97-1.82 (m, 4H), 1.73-1.61 (m, 2H), 1.48 (dt, J = 7.06, 1.18 Hz, 3H).

EXAMPLE 133

5-Chloro-1,1-dioxido-2-(4-(4-(6-fluoro-2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one

mp 155-156 °C ^{1}H NMR (400 MHz, $CDCl_3$) 8.04 (dd, 1H), 7.89 - 7.82 (m, 2H), 7.18 (q, 1H), 7.00 (dd, 1H), 6.89 (td, 1H), 4.19 (m, 1H), 3.82

(t, 2H), 3.07 (d, 2H), 2.45 (t, 2H), 2.40-2.27 (m, 2H), 2.11 (td, 2H), 1.97-1.82 (m, 4H), 1.64 (m, 2H).

EXAMPLE 134

4-Methyl-1,1-dioxido-2-(4-(4-(2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one

mp 137-138 °C ^{1}H NMR (400 MHz, $CDCl_3$) 7.78-7.69 (m, 2H), 7.58 (d, J = 7.5 Hz, 1H), 7.27 (d, J = 4.7 Hz, 1H), 7.20 (dd, J = 6.9 Hz, 1.4 Hz, 1H), 7.17-7.06 (m, 2H), 4.21 (m, 1H), 3.81 (t, J = 14.8 Hz, 2H), 3.07 (d, J = 11.6 Hz, 2H), 2.79 (s, 3H), 2.46 (t, J = 14.8 Hz, 2H), 2.41-2.31 (m, 2H), 2.12 (t, J = 23.8 Hz, 2H), 1.97-1.81 (m, 4H), 1.69-1.59 (m, 2H).

EXAMPLE 135

4-Chloro-1,1-dioxido-2-(4-(4-(2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one

mp 178-180 °C ^{1}H NMR (400 MHz, $CDCl_3$) 7.88-7.84 (m, 1H), 7.82-7.76 (m, 2H), 7.31-7.26 (m, 1H), 7.24-7.08 (m, 3H), 4.21 (m, 1H), 3.84 (t, J = 14.6 Hz, 2H), 3.09 (d, J = 9.6 Hz, 2H), 2.46 (t, J = 14.5 Hz, 2H), 2.43-2.33 (m, 2H), 2.12 (t, J = 23.8 Hz, 2H), 1.99-1.83 (m, 4H), 1.71-1.59 (m, 2H).

EXAMPLE 136

4-Ethoxy-1,1-dioxido-2-(4-(4-(2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one

^{1}H NMR (400 MHz, $CDCl_3$), 7.77 (t, J = 7.6 Hz, 1H), 7.45 (d, J = 8.0 Hz, 1H), 7.28-7.27 (m, 2H), 7.19 (d, J = 7.6 Hz, 1H), 7.15 (t, J = 7.6 Hz, 1H), 7.08 (td, J = 7.6, 1.4 Hz, 1H), 4.28 (q, J = 7.0 Hz, 2H), 4.26 (tt, J = 12.6, 4.2 Hz, 1H), 3.78 (t, J = 7.4 Hz, 2H), 3.07 (d, J = 11.6 Hz, 2H), 2.44 (t, J = 7.2 Hz, 2H), 2.36 (td, J = 12.5, 3.7 Hz, 2H), 2.11 (td, J

= 12.0, 1.6 Hz, 2H), 1.93-1.83 (m, 4H), 1.63 (qn, J = 7.6 Hz, 2H), 1.55 (t, J = 7.0 Hz, 3H).

EXAMPLE 137

4-(2-Propyloxy)-1,1-dioxido-2-(4-(4-(2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one

^{1}H NMR (400 MHz, $CDCl_3$) 7.75 (dd, J = 8.4, 7.7 Hz, 1H), 7.43 (d, J = 7.5 Hz, 1H), 7.27 (d, J = 7.9 Hz, 1H), 7.26 (d, J = 8.6 Hz, 1H), 7.19 (dd, J = 7.8, 1.2 Hz, 1H), 7.14 (td, J = 7.7, 1.3 Hz, 1H), 7.08 (td, J = 7.8, 1.2 Hz, 1H), 4.77 (sept., J = 6.0 Hz, 1H), 4.21 (tt, J = 12.5, 4.3 Hz, 1H), 3.77 (t, J = 7.4 Hz, 2H), 3.07 (d, J = 11.7 Hz, 2H), 2.44 (t , J = 7.3 Hz, 2H), 2.36 (td, J = 12.6, 3.8 Hz, 2H), 2.11 (td, J = 11.9, 1.8 Hz, 2H), 1.94-1.83 (m, 4H), 1.63 (qn, J = 7.5 Hz, 2H), 1.47 (d, J = 6.0 Hz, 6H).

EXAMPLE 138

5-Methoxy-1,1-dioxido-2-(4-(4-(6-methyl-2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one

^{1}H NMR (400 MHz, $CDCl_3$) 7.81 (d, J = 8.6 Hz, 1H), 7.77 (d, J = 8.1 Hz, 1H), 7.48 (d, J = 2.2 Hz, 1H), 7.33 (dd, J = 8.6, 2.4 Hz, 1H), 7.07 (d, J = 7.9 Hz, 1H), 7.03 (s, 1H), 4.56 (t, J = 12.6 Hz, 1H), 3.97 (s, 3H), 3.83 (t, J = 6.6 Hz, 2H), 3.72 (d, J = 11.0 Hz, 2H), 3.25 (m, 2H), 3.11 (m, 2H), 2.90 (m, 2H), 2.37 (s, 3H), 2.09-1.96 (m, 6H).

EXAMPLE 139

1,1-Dioxido-2-(4-(4-(2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-6-methylsulfonyl-1,2-benzisothiazol-3(2H)-one

^{1}H NMR (400 MHz, $CDCl_3$) 8.51 (s, 1H), 8.40 (d, J = 9.57 Hz, 1H), 8.27 (d, J = 7.89 Hz, 1H), 7.20 (d, J = 7.73 Hz, 1H), 7.16-7.08 (m, 3H), 4.21 (m, 1H), 3.89 (t, J = 7.39 Hz, 2H), 3.17 (s, 3H), 3.12 (bd, 2H),

2.40 (s, 2H), 2.37 (d, 2H), 1.93 (t, J = 7.73 Hz, 2H), 1.87 (bd, 2H), 1.60 (bm, 4H).

EXAMPLE 140

5-Methoxy-1,1-dioxido-2-(4-(4-(2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one

^{1}H NMR (400 MHz, $CDCl_3$) 7.93 (d, J = 7.87 Hz, 1H), 7.82 (d, J = 8.60 Hz, 1H), 7.48 (d, J = 2.38 Hz, 1H), 7.34 (dd, J = 6.22, 2.38 Hz, 1H), 7.27 (m, 1H), 7.20 (d, J = 7.14, 1H), 7.13 (t, J = 7.69 Hz, 1H), 4.60 (tt, J = 12.81, 4.03 Hz, 1H), 3.97 (s, 3H), 3.83 (t, J = 6.59 Hz, 2H), 3.74 (d, J = 12.09 Hz, 2H), 3.32 (dq, J = 12.82, 4.03 Hz, 2H), 3.12 (br t, J = 4.58 Hz, 2H), 2.92 (br q, J = 10.07 Hz, 2H), 2.14-1.95 (m, 6H).

EXAMPLE 141

1,1-Dioxido-2-(4-(4-(2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-5-methylsulfonyl-1,2-benzisothiazol-3(2H)-one

^{1}H NMR (400 MHz, DMSO-d_6) 8.67 (d, J = 8.06 Hz, 1H), 8.57 (dd, J = 8.06, 1.51 Hz, 1H), 8.54 (s, 1H), 7.39 (m, 2H), 7.26 (t, J = 7.88 Hz, 1H), 7.17 (t, J = 7.72 Hz, 1H), 4.49 (dt, J = 11.92, 4.01 Hz, 1H), 3.85 (bm, 2H), 3.64 (br d, J = 11.92 Hz, 2H), 3.44 (s, 3H), 3.20-3.10 (m, 2H), 2.54 (m, 2H), 2.08 (br d, J = 12.59 Hz, 2H).

EXAMPLE 142

5-Methylthio-1,1-dioxido-2-(4-(4-(2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one

^{1}H NMR (400 MHz, $CDCl_3$) 7.93 (d, J = 7.87 Hz, 1H), 7.77 (m, 2H), 7.63 (dd, J = 8.24, 1.83 Hz, 1H), 7.27 (m, 1H), 7.20 (dd, J = 8.05, 1.10 Hz, 1H), 7.13 (t, J = 8.42, 0.92 Hz, 1H), 4.60 (dt, J = 12.81, 4.22 Hz, 1H), 3.84 (t, J = 6.59 Hz, 2H), 3.74 (br d, J = 11.54 Hz, 2H), 3.33 (dq, J

= 13.55, 3.84 Hz, 2H), 3.13 (m, 2H), 2.93 (q, J = 10.07 Hz, 2H), 2.60 (s, 3H), 2.14-1.93 (m, 6H).

EXAMPLE 143

5-Methylsulfonyl-1,1-dioxido-2-(4-(4-(6-methyl-2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one

^{1}H NMR (400 MHz, $CDCl_3$) 8.63 (s, 1H), 8.46 (dd, J = 8.05, 1.65 Hz, 1H), 8.15 (dd, J = 8.05, 0.55 Hz, 1H), 7.13 (d, J = 8.06 Hz, 1H), 7.03 (s, 1H), 6.95 (d, J = 8.05 Hz, 1H), 4.18 (dt, J = 12.01, 4.21 Hz, 1H), 3.89 (t, J = 7.33 Hz, 2H), 3.16 (s, 3H), 3.07 (br d, J = 10.99 Hz, 2H), 2.46 (t, J = 7.14 Hz, 2H), 2.38 (s, 3H), 2.34 (m, 2H), 2.11 (t, J = 11.17 Hz, 2H), 1.97-1.84 (m, 6H).

EXAMPLE 144

1,1-Dioxido-2-(4-(4-(2-oxo-1-oxazolo[5,4-b]pyridyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one

^{1}H NMR (400 MHz, $CDCl_3$) 8.38 (d, J = 7.51 Hz, 1H), 8.07 (m, 2H), 7.91 (m, 3H), 7.25 (m, 1H), 4.64 (m, 1H), 3.86 (t, J = 3.20 Hz, 2H), 3.74 (br d, J = 10.99 Hz, 2H), 3.29 (m, 2H), 3.13 (bs, 2H), 2.92 (m, 2H), 2.18-1.99 (m, 6H).

SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i) APPLICANT: Thompson, Wayne J.
Huff, Joel R.
Nerenberg, Jennie B.
Lee, Hee-Yoon
Bell, Ian M.

(ii) TITLE OF INVENTION: ALPHA1C ADRENERGIC RECEPTOR ANTAGONISTS

(iii) NUMBER OF SEQUENCES: 35

(iv) CORRESPONDENCE ADDRESS:
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(B) STREET: 126 Lincoln Avenue
(C) CITY: Rahway
(D) STATE: New Jersey
(E) COUNTRY: United States of America
(F) ZIP: 07065

(v) COMPUTER READABLE FORM:
(A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: PatentIn Release #1.0, Version #1.25

(vi) CURRENT APPLICATION DATA:
(A) APPLICATION NUMBER:
(B) FILING DATE:
(C) CLASSIFICATION:

(vii) PRIOR APPLICATION DATA:
(A) APPLICATION NUMBER: 08/229,276
(B) FILING DATE: 14-APR-1995

(viii) ATTORNEY/AGENT INFORMATION:
(A) NAME: Appollina, Mary A.
(B) REGISTRATION NUMBER: 34,087
(C) REFERENCE/DOCKET NUMBER: 19169Y

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(A) TELEPHONE: (908)594-3462
(B) TELEFAX: (908)594-4720
(C) TELEX: 138825

(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 28 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: both

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

TTTTCTAGAT TRTTNARRTA NCCNAGCC 28

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 26 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

TTTACTAGTA TCSTNGTNAT GTAYTG 26

(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 26 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

TTTTCTAGAG AARAANGGNA RCCARC 26

(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 235 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: both
(D) TOPOLOGY: both

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

```
GCCGCGTCTA CGTGGTGGCC AAGAGGGAGA GCCGGGGCCT CAAGTCTGGC CTCAAGACCG    60

ACAAGTCGGA CTCGGAGCAA GTGACGCTCC GCATCCATCG GAAAAACGCC CCGGCAGGAG   120

GCAGCGGGAT GGCCAGCGCC AAGACCAAGA CGCACTTCTC AGTGAGGCTC CTCAAGTTCT   180

CCCGGGAGAA GAAAGCGGCC AAAACGCTGG GCATCGTGGT CGGCTGCTTC GTCCT        235
```

(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 78 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

```
Arg Val Tyr Val Val Ala Lys Arg Glu Ser Arg Gly Leu Lys Ser Gly
1               5                   10                  15

Leu Lys Thr Asp Lys Ser Asp Ser Glu Gln Val Thr Leu Arg Ile His
            20                  25                  30

Arg Lys Asn Ala Pro Ala Gly Gly Ser Gly Met Ala Ser Ala Lys Thr
        35                  40                  45

Lys Thr His Phe Ser Val Arg Leu Leu Lys Phe Ser Arg Glu Lys Lys
    50                  55                  60
```

Ala Ala Lys Thr Leu Gly Ile Val Val Gly Cys Phe Val Leu
65 70 75

(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 93 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

Leu Val Met Tyr Cys Arg Val Tyr Val Val Ala Lys Arg Glu Ser Arg
1 5 10 15

Gly Leu Lys Ser Gly Leu Lys Thr Asp Lys Ser Asp Ser Glu Gln Val
20 25 30

Thr Leu Arg Ile His Arg Lys Asn Ala Gln Val Gly Gly Ser Gly Val
35 40 45

Thr Ser Ala Lys Asn Lys Thr His Phe Ser Val Arg Leu Leu Lys Phe
50 55 60

Ser Arg Glu Lys Lys Ala Ala Lys Thr Leu Gly Ile Val Val Gly Cys
65 70 75 80

Phe Val Leu Cys Trp Leu Pro Phe Phe Leu Val Met Pro
85 90

(2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1601 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: both
(D) TOPOLOGY: both

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

```
GAATTCCCTC CTAGAAGCTG GAGAGAGCAG GAGCCTTCGG TGGGGCAGCT CAAAATGTAG     60
GTAACTGCGG GCCAGGAGCA GCGCCCAGAT GCCATCGGTC CCTGCCTTTG AGCGTCGACG    120
GCTGATCTTT TGGTTTGAGG GAGAGACTGG CGCTGGAGTT TTGAATTCCG AATCATGTGC    180
AGAATCGTGA ATCTTCCCCC AGCCAGGACG AATAAGACAG CGCGGAAAAG CAGATTCTCG    240
TAATTCTGGA ATTGCATGTT GCAAGGAGTC TCCTGGATCT TCGCACCCAG CTTCGGGTAC    300
GGGAGGGAGT CCGGGTCCCG GCTAGGCCAG CCCGCAGGTG GAGAGGGTCC CCGGCAGCCC    360
CGCGCGCCCC TGGCCATGTC TTTAATGCCC TGCCCCTTCA TGTGGCCTTC TGAGGGTTCC    420
CAGGGCTGGC CAGGGTTGTC TCCCACCCGC GCGCGCCGTC TCACCCCCAG CCAAACCCAC    480
CTGGCAGGGC TCCCTCCAGA AGAGACCTTT TGATTCCCGG CTCCCGCGCT CCCGCCTCCG    540
CGCCAGCCCG GGAGGTGGCC CTGGACAGCC GGACCTCGCC CGGCCCCGGC TGGGACCATG    600
GTGTTTCTCT CGGGAAATGC TTCCGACAGC TCCAACTGCA CCCAACCGCC GGCACCGGTG    660
AACATTTCCA AGGCCATTCT GCTCGGGGTG ATCTTGGGGG GCCTCATTCT TTTCGGGGTG    720
CTGGGTAACA TCCTAGTGAT CCTCTCCGTA GCCTGTCACC GACACCTGCA CTCAGTCACG    780
CACTACTACA TCGTCAACCT GGCGGTGGCC GACCTCCTGC TCACCTCCAC GGTGCTGCCC    840
TTCTCCGCCA TCTTCGAGGT CCTAGGCTAC TGGGCCTTCG GCAGGGTCTT CTGCAACATC    900
TGGGCGGCAG TGGATGTGCT GTGCTGCACC GCGTCCATCA TGGGCCTCTG CATCATCTCC    960
ATCGACCGCT ACATCGGCGT GAGCTACCCG CTGCGCTACC CAACCATCGT CACCCAGAGG   1020
AGGGGTCTCA TGGCTCTGCT CTGCGTCTGG GCACTCTCCC TGGTCATATC CATTGGACCC   1080
CTCTTCGGCT GGAGGCAGCC GGCCCCCGAG GACGAGACCA TCTGCCAGAT CAACGAGGAG   1140
CCGGGCTACG TGCTCTTCTC GGCTCTGGGC TCCTTCTACC TGCCTCTGGC CATCATCCTG   1200
GTCATGTACT GCCGCGTCTA CGTGGTGGCC AAGAGGGAGA GCCGGGGCCT CAAGTCTGGC   1260
CTCAAGACCG ACAAGTCGGA CTCGGAGCAA GTGACGCTCC GCATCCATCG GAAAAACGCC   1320
CCGGCAGGAG GCAGCGGGAT GGCCAGCGCC AAGACCAAGA CGCACTTCTC AGTGAGGCTC   1380
CTCAAGTTCT CCCGGGAGAA GAAAGCGGCC AAAACGCTGG GCATCGTGGT CGGCTGCTTC   1440
GTCCTCTGCT GGCTGCCTTT TTTCTTAGTC ATGCCCATTG GGTCTTTCTT CCCTGATTTC   1500
AAGCCCTCTG AAACAGTTTT TAAAATAGTA TTTTGGCTCG GATATCTAAA CAGCTGCATC   1560
AACCCCATCA TATACCCATG CTCCAGCCAA GAGGGAATTC C                        1601
```

(2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 26 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

TTTGAATTCT GATTTCAAGC CCTCTG 26

(2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

TTTGAATTCT TANACYTCYT CNCCRTTYTC 30

(2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 512 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: both
(D) TOPOLOGY: both

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

CTGATTTCAA GCCCTCTGAA ACAGTTTTTA AAATAGTATT TTGGCTCGGA TATCTAAACA 60

GCTGCATCAA CCCCATCATA TACCCATGCT CCAGCCAAGA GTTCAAAAAG GCCTTTCAGA 120

ATGTCTTGAG AATCCAGTGT CTCCGCAGAA AGCAGTCTTC CAAACATGCC CTGGGCTACA 180

CCCTGCACCC GCCCAGCCAG GCCGTGGAAG GGCAACACAA GGACATGGTG CGCATCCCCG 240

TGGGATCAAG AGAGACCTTC TACAGGATCT CCAAGACGGA TGGCGTTTGT GAATGGAAAT 300

TTTTCTCTTC CATGCCCCGT GGATCTGCCA GGATTACAGT GTCCAAAGAC CAATCCTCCT 360

GTACCACAGC CCGGGTGAGA AGTAAAAGCT TTTTGCAGGT CTGCTGCTGT GTAGGGCCCT 420

CAACCCCCAG CCTTGACAAG AACCATCAAG TTCCAACCAT TAAGGTCCAC ACCATCTCCC 480

TCAGTGAGAA CGGCGAAGAG GTTTAAGAAT TC 512

(2) INFORMATION FOR SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 2004 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: both
(D) TOPOLOGY: both

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

GAATTCCCTC CTAGAAGCTG GAGAGAGCAG GAGCCTTCGG TGGGGCAGCT CAAAATGTAG 60

GTAACTGCGG GCCAGGAGCA GCGCCCAGAT GCCATCGGTC CCTGCCTTTG AGCGTCGACG 120

GCTGATCTTT TGGTTTGAGG GAGAGACTGG CGCTGGAGTT TTGAATTCCG AATCATGTGC 180

AGAATCGTGA ATCTTCCCCC AGCCAGGACG AATAAGACAG CGCGGAAAAG CAGATTCTCG 240

TAATTCTGGA ATTGCATGTT GCAAGGAGTC TCCTGGATCT TCGCACCCAG CTTCGGGTAC 300

GGGAGGGAGT CCGGGTCCCG GCTAGGCCAG CCCGCAGGTG GAGAGGGTCC CCGGCAGCCC 360

CGCGCGCCCC TGGCCATGTC TTTAATGCCC TGCCCCTTCA TGTGGCCTTC TGAGGGTTCC 420

CAGGGCTGGC CAGGGTTGTC TCCCACCCGC GCGCGCCGTC TCACCCCCAG CCAAACCCAC 480

CTGGCAGGGC TCCCTCCAGA AGAGACCTTT TGATTCCCGG CTCCCGCGCT CCCGCCTCCG 540

CGCCAGCCCG GGAGGTGGCC CTGGACAGCC GGACCTCGCC CGGCCCCGGC TGGGACCATG 600

GTGTTTCTCT CGGGAAATGC TTCCGACAGC TCCAACTGCA CCCAACCGCC GGCACCGGTG 660

AACATTTCCA AGGCCATTCT GCTCGGGGTG ATCTTGGGGG GCCTCATTCT TTTCGGGGTG 720

CTGGGTAACA TCCTAGTGAT CCTCTCCGTA GCCTGTCACC GACACCTGCA CTCAGTCACG 780

CACTACTACA TCGTCAACCT GGCGGTGGCC GACCTCCTGC TCACCTCCAC GGTGCTGCCC 840

TTCTCCGCCA TCTTCGAGGT CCTAGGCTAC TGGGCCTTCG GCAGGGTCTT CTGCAACATC 900

TGGGCGGCAG TGGATGTGCT GTGCTGCACC GCGTCCATCA TGGGCCTCTG CATCATCTCC 960

ATCGACCGCT ACATCGGCGT GAGCTACCCG CTGCGCTACC CAACCATCGT CACCCAGAGG 1020

AGGGGTCTCA TGGCTCTGCT CTGCGTCTGG GCACTCTCCC TGGTCATATC CATTGGACCC 1080

CTCTTCGGCT GGAGGCAGCC GGCCCCCGAG GACGAGACCA TCTGCCAGAT CAACGAGGAG 1140

CCGGGCTACG TGCTCTTCTC GGCTCTGGGC TCCTTCTACC TGCCTCTGGC CATCATCCTG 1200

GTCATGTACT GCCGCGTCTA CGTGGTGGCC AAGAGGGAGA GCCGGGGCCT CAAGTCTGGC 1260

CTCAAGACCG ACAAGTCGGA CTCGGAGCAA GTGACGCTCC GCATCCATCG GAAAAACGCC 1320

CCGGCAGGAG GCAGCGGGAT GGCCAGCGCC AAGACCAAGA CGCACTTCTC AGTGAGGCTC 1380

CTCAAGTTCT CCCGGGAGAA GAAAGCGGCC AAAACGCTGG GCATCGTGGT CGGCTGCTTC 1440

GTCCTCTGCT GGCTGCCTTT TTTCTTAGTC ATGCCCATTG GGTCTTTCTT CCCTGATTTC 1500

AAGCCCTCTG AAACAGTTTT TAAAATAGTA TTTTGGCTCG GATATCTAAA CAGCTGCATC 1560

AACCCCATCA TATACCCATG CTCCAGCCAA GAGTTCAAAA AGGCCTTTCA GAATGTCTTG 1620

AGAATCCAGT GTCTCCGCAG AAAGCAGTCT TCCAAACATG CCCTGGGCTA CACCCTGCAC 1680

CCGCCCAGCC AGGCCGTGGA AGGGCAACAC AAGGACATGG TGCGCATCCC CGTGGGATCA 1740

AGAGAGACCT TCTACAGGAT CTCCAAGACG GATGGCGTTT GTGAATGGAA ATTTTTCTCT 1800

TCCATGCCCC GTGGATCTGC CAGGATTACA GTGTCCAAAG ACCAATCCTC CTGTACCACA 1860

GCCCGGGTGA GAAGTAAAAG CTTTTTGCAG GTCTGCTGCT GTGTAGGGCC CTCAACCCCC 1920

AGCCTTGACA AGAACCATCA AGTTCCAACC ATTAAGGTCC ACACCATCTC CCTCAGTGAG 1980

AACGGCGAAG AGGTTTAAGA ATTC 2004

(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 466 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: N-terminal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

```
Met Val Phe Leu Ser Gly Asn Ala Ser Asp Ser Ser Asn Cys Thr Gln
1               5                   10                  15

Pro Pro Ala Pro Val Asn Ile Ser Lys Ala Ile Leu Leu Gly Val Ile
            20                  25                  30

Leu Gly Gly Leu Ile Leu Phe Gly Val Leu Gly Asn Ile Leu Val Ile
        35                  40                  45

Leu Ser Val Ala Cys His Arg His Leu His Ser Val Thr His Tyr Tyr
    50                  55                  60

Ile Val Asn Leu Ala Val Ala Asp Leu Leu Leu Thr Ser Thr Val Leu
65                  70                  75                  80

Pro Phe Ser Ala Ile Phe Glu Val Leu Gly Tyr Trp Ala Phe Gly Arg
                85                  90                  95

Val Phe Cys Asn Ile Trp Ala Ala Val Asp Val Leu Cys Cys Thr Ala
            100                 105                 110

Ser Ile Met Gly Leu Cys Ile Ile Ser Ile Asp Arg Tyr Ile Gly Val
        115                 120                 125

Ser Tyr Pro Leu Arg Tyr Pro Thr Ile Val Thr Gln Arg Arg Gly Leu
    130                 135                 140

Met Ala Leu Leu Cys Val Trp Ala Leu Ser Leu Val Ile Ser Ile Gly
145                 150                 155                 160

Pro Leu Phe Gly Trp Arg Gln Pro Ala Pro Glu Asp Glu Thr Ile Cys
                165                 170                 175

Gln Ile Asn Glu Glu Pro Gly Tyr Val Leu Phe Ser Ala Leu Gly Ser
            180                 185                 190

Phe Tyr Leu Pro Leu Ala Ile Ile Leu Val Met Tyr Cys Arg Val Tyr
        195                 200                 205

Val Val Ala Lys Arg Glu Ser Arg Gly Leu Lys Ser Gly Leu Lys Thr
    210                 215                 220

Asp Lys Ser Asp Ser Glu Gln Val Thr Leu Arg Ile His Arg Lys Asn
225                 230                 235                 240
```

```
Ala Pro Ala Gly Gly Ser Gly Met Ala Ser Ala Lys Thr Lys Thr His
                245                 250                 255

Phe Ser Val Arg Leu Leu Lys Phe Ser Arg Glu Lys Lys Ala Ala Lys
            260                 265                 270

Thr Leu Gly Ile Val Val Gly Cys Phe Val Leu Cys Trp Leu Pro Phe
        275                 280                 285

Phe Leu Val Met Pro Ile Gly Ser Phe Phe Pro Asp Phe Lys Pro Ser
    290                 295                 300

Glu Thr Val Phe Lys Ile Val Phe Trp Leu Gly Tyr Leu Asn Ser Cys
305                 310                 315                 320

Ile Asn Pro Ile Ile Tyr Pro Cys Ser Ser Gln Glu Phe Lys Lys Ala
                325                 330                 335

Phe Gln Asn Val Leu Arg Ile Gln Cys Leu Arg Arg Lys Gln Ser Ser
            340                 345                 350

Lys His Ala Leu Gly Tyr Thr Leu His Pro Pro Ser Gln Ala Val Glu
        355                 360                 365

Gly Gln His Lys Asp Met Val Arg Ile Pro Val Gly Ser Arg Glu Thr
    370                 375                 380

Phe Tyr Arg Ile Ser Lys Thr Asp Gly Val Cys Glu Trp Lys Phe Phe
385                 390                 395                 400

Ser Ser Met Pro Arg Gly Ser Ala Arg Ile Thr Val Ser Lys Asp Gln
                405                 410                 415

Ser Ser Cys Thr Thr Ala Arg Val Arg Ser Lys Ser Phe Leu Gln Val
            420                 425                 430

Cys Cys Cys Val Gly Pro Ser Thr Pro Ser Leu Asp Lys Asn His Gln
        435                 440                 445

Val Pro Thr Ile Lys Val His Thr Ile Ser Leu Ser Glu Asn Gly Glu
    450                 455                 460

Glu Val
465
```

(2) INFORMATION FOR SEQ ID NO:13:

(i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 1621 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: both

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

```
CCCGTGCAGG GGCCCTACGG ACACCACCAG GGCTACGACC CAGAGCAGGG CCAGGATGGC     60
GGCCGCCTTG CGCTCGGTCA TGATGGCTGG GTACTTGAGT GAGTGGCGCA CGCCCACGTA    120
CCGGTCCACG GAGATGGTGC AGAGGCTGAG GATGGAGGCC GTGCAGCACA GCACGTCCAC    180
GGCGGCCGTC GGGGGACTGG TGGTGAGCGC GCAGGGCGTG GGCGTGGGCG TCTTCCTGGC    240
AGCCTTCATC CTTATGGCCG TGGCAGGTAA CCTGCTTGTC ATCCTCTCAG TGGCCTGCAA    300
CCGCCACCTG CAGACCGTCA CCAACTATTT CATCGTGAAC CTGGCCGTGG CCGACCTGCT    360
GCTGAGCGCC ACCGTACTGC CCTTCTCGGC CACCATGGAG GTTCTGGGCT TCTGGGCCTT    420
TGGCCGCGCC TTCTGCGACG TATGGGCCGC CGTGGACGTG CTGTGCTGCA CGGCCTCCAT    480
CCTCAGCCTC TGCACCATCT CCGTGGACCG GTACGTGGGC GTGCGCCACT CACTCAAGTA    540
CCCAGCCATC ATGACCGAGC GCAAGGCGGC CGCCATCCTG GCCCTGCTCT GGGTCGTAGC    600
CCTGGTGGTG TCCGTAGGGC CCCTGCTGGG CTGGAAGGAG CCCGTGCCCC CTGACGAGCG    660
CTTCTGCGGT ATCACCGAGG AGGCGGGCTA CGCTGTCTTC TCCTCCGTGT GCTCCTTCTA    720
CCTGCCCATG GCGGTCATCG TGGTCATGTA CTGCCGCGTG TACGTGGTCG CGCGCAGCAC    780
CACGCGCAGC CTCGAGGCAG GCGTCAAGCG CGAGCGAGGC AAGGCCTCCG AGGTGGTGCT    840
GCGCATCCAC TGTCGCGGCG CGGCCACGGG CGCCGACGGG GCGCACGGCA TGCGCAGCGC    900
CAAGGGCCAC ACCTTCCGCA GCTCGCTCTC CGTGCGCCTG CTCAAGTTCT CCCGTGAGAA    960
GAAAGCGGCC AAGACTCTGG CCATCGTCGT GGGTGTCTTC GTGCTCTGCT GGTTCCCTTT   1020
CTTCTTTGTC CTGCCGCTCG GCTCCTTGTT CCCGCAGCTG AAGCCATCGG AGGGCGTCTT   1080
CAAGGTCATC TTCTGGCTCG GCTACTTCAA CAGCTGCGTG AACCCGCTCA TCTACCCCTG   1140
TTCCAGCCGC GAGTTCAAGC GCGCCTTCCT CCGTCTCCTG CGCTGCCAGT GCCGTCGTCG   1200
CCGGCGCCGC CGCCCTCTCT GGCGTGTCTA CGGCCACCAC TGGCGGGCCT CCACCAGCGG   1260
CCTGCGCCAG GACTGCGCCC CGAGTTCGGG CGACGCGCCC CCCGGAGCGC CGCTGGCCCT   1320
CACCGCGCTC CCCGACCCCG ACCCCGAACC CCCAGGCACG CCCGAGATGC AGGCTCCGGT   1380
CGCCAGCCGT CGAAGCCACC CAGCGCCTTC CGCGAGTGGA GGCTGCTGGG GCCGTTCCGG   1440
AGACCCACGA CCCAGCTGCG CGCCAAAGTC GCCAGCCTGT CGCACAAGAT CGCCGCCGGG   1500
```

GGCGCGCAGC GCGCAGAGGC AGCGTGCGCC CAGCGCTCAG AGGTGGAGGC TGTGTCCCTA 1560

GGCGTCCCAC ACGAGGTGGC CGAGGGCGCC ACCTGCCAGG CCTACGAATT GGCCGACTAC 1620

A 1621

(2) INFORMATION FOR SEQ ID NO:14:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 501 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: N-terminal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

Met Ala Ala Ala Leu Arg Ser Val Met Met Ala Gly Tyr Leu Ser Glu
1 5 10 15

Trp Arg Thr Pro Thr Tyr Arg Ser Thr Glu Met Val Gln Arg Leu Arg
20 25 30

Met Glu Ala Val Gln His Ser Thr Ser Thr Ala Ala Val Gly Gly Leu
35 40 45

Val Val Ser Ala Gln Gly Val Gly Val Gly Val Phe Leu Ala Ala Phe
50 55 60

Ile Leu Met Ala Val Ala Gly Asn Leu Leu Val Ile Leu Ser Val Ala
65 70 75 80

Cys Asn Arg His Leu Gln Thr Val Thr Asn Tyr Phe Ile Val Asn Leu
85 90 95

Ala Val Ala Asp Leu Leu Leu Ser Ala Thr Val Leu Pro Phe Ser Ala
100 105 110

Thr Met Glu Val Leu Gly Phe Trp Ala Phe Gly Arg Ala Phe Cys Asp
115 120 125

Val Trp Ala Ala Val Asp Val Leu Cys Cys Thr Ala Ser Ile Leu Ser
130 135 140

Leu Cys Thr Ile Ser Val Asp Arg Tyr Val Gly Val Arg His Ser Leu
145 150 155 160

Lys Tyr Pro Ala Ile Met Thr Glu Arg Lys Ala Ala Ala Ile Leu Ala
165 170 175

Leu Leu Trp Val Val Ala Leu Val Val Ser Val Gly Pro Leu Leu Gly
180 185 190

Trp Lys Glu Pro Val Pro Pro Asp Glu Arg Phe Cys Gly Ile Thr Glu
195 200 205

Glu Ala Gly Tyr Ala Val Phe Ser Ser Val Cys Ser Phe Tyr Leu Pro
210 215 220

Met Ala Val Ile Val Val Met Tyr Cys Arg Val Tyr Val Val Ala Arg
225 230 235 240

Ser Thr Thr Arg Ser Leu Glu Ala Gly Val Lys Arg Glu Arg Gly Lys
245 250 255

Ala Ser Glu Val Val Leu Arg Ile His Cys Arg Gly Ala Ala Thr Gly
260 265 270

Ala Asp Gly Ala His Gly Met Arg Ser Ala Lys Gly His Thr Phe Arg
275 280 285

Ser Ser Leu Ser Val Arg Leu Leu Lys Phe Ser Arg Glu Lys Lys Ala
290 295 300

Ala Lys Thr Leu Ala Ile Val Val Gly Val Phe Val Leu Cys Trp Phe
305 310 315 320

Pro Phe Phe Phe Val Leu Pro Leu Gly Ser Leu Phe Pro Gln Leu Lys
325 330 335

Pro Ser Glu Gly Val Phe Lys Val Ile Phe Trp Leu Gly Tyr Phe Asn
340 345 350

Ser Cys Val Asn Pro Leu Ile Tyr Pro Cys Ser Ser Arg Glu Phe Lys
355 360 365

Arg Ala Phe Leu Arg Leu Leu Arg Cys Gln Cys Arg Arg Arg Arg Arg
370 375 380

Arg Arg Pro Leu Trp Arg Val Tyr Gly His His Trp Arg Ala Ser Thr
385 390 395 400

Ser Gly Leu Arg Gln Asp Cys Ala Pro Ser Ser Gly Asp Ala Pro Pro
405 410 415

Gly Ala Pro Leu Ala Leu Thr Ala Leu Pro Asp Pro Asp Pro Glu Pro
420 425 430

```
Pro Gly Thr Pro Glu Met Gln Ala Pro Val Ala Ser Arg Arg Ser His
        435                 440                 445

Pro Ala Pro Ser Ala Ser Gly Gly Cys Trp Gly Arg Ser Gly Asp Pro
    450                 455                 460

Arg Pro Ser Cys Ala Pro Lys Ser Pro Ala Cys Arg Thr Arg Ser Pro
465                 470                 475                 480

Pro Gly Ala Arg Ser Ala Gln Arg Gln Arg Ala Pro Ser Ala Gln Arg
                485                 490                 495

Trp Arg Leu Cys Pro
            500
```

(2) INFORMATION FOR SEQ ID NO:15:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

TCTAGACCAT GAAYCCNGAY CTGG 24

(2) INFORMATION FOR SEQ ID NO:16:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

TTTGAATTCA CATWCCGACY ACAATGCCC 29

(2) INFORMATION FOR SEQ ID NO:17:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 921 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: both

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

TCTAGACCAT GAATCCCGAC CTGGACACCG GCCACAACAC ATCAGCACCT GCCCACTGGG 60

GAGAGTTGAA AAATGCCAAC TTCACTGGCC CCAACCAGAC CTCGAGCAAC TCCACACTGC 120

CCCAGCTGGA CATCACCAGG GCCATCTCTG TGGGCCTGGT GCTGGGCGCC TTCATCCTCT 180

TTGCCATCGT GGGCAACATC CTAGTCATCT TGTCTGTGGC CTGCAACCGG CACCTGCGGA 240

CGCCCACCAA CTACTTCATT GTCAACCTGG CCATGGCCGA CCTGCTGTTG AGCTTCACCG 300

TCCTGCCCTT CTCAGCGGCC CTAGAGGTGC TCGGCTACTG GGTGCTGGGG CGGATCTTCT 360

GTGACATCTG GGCAGCCGTG GATGTCCTGT GCTGCACAGC GTCCATTCTG AGCCTGTGCG 420

CCATCTCCAT CGATCGCTAC ATCGGGGTGC GCTACTCTCT GCAGTATCCC ACGCTGGTCA 480

CCCGGAGGAA GGCCATCTTG GCCCTGCTCA GTGTCTGGGT CTTGTCCACC GTCATCTCCA 540

TCGGGCCTCT CCTTGGGTGG AAGGAGCCGG CACCCAACGA TGACAAGGAG TGCGGGGTCA 600

CCGAAGAACC CTTCTATGCC CTCTTCTCCT CTCTGGGCTC CTTCTACATC CCTCTGGCGG 660

TCATTCTAGT CATGTACTGC CGTGTCTATA TAGTGGCCAA GAGAACCACC AAGAACCTAG 720

AGGCAGGAGT CATGAAGGAG ATGTCCAACT CCAAGGAGCT GACCCTGAGG ATCCATTCCA 780

AGAACTTTCA CGAGGACACC CTTAGCAGTA CCAAGGCCAA GGGCCACAAC CCCAGGAGTT 840

CCATAGCTGT CAAACTTTTT AAGTTCTCCA GGGAAAAGAA AGCAGCTAAG ACGTTGGGCA 900

TTGTGGTCGG TATGTGAATT C 921

(2) INFORMATION FOR SEQ ID NO:18:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

GAAGGCGCGC TTGAACTC 18

(2) INFORMATION FOR SEQ ID NO:19:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

AGAGAACCAC CAAGAACC 18

(2) INFORMATION FOR SEQ ID NO:20:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 389 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: both
(D) TOPOLOGY: both

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

AAGAGAACCA CCAAGAACCT AGAGGCAGGA GTCATGAAGG AGATGTCCAA CTCCAAGGAG 60

CTGACCCTGA GGATCCATTC CAAGAACTTT CACGAGGACA CCCTTAGCAG TACCAAGGCC 120

AAGGGCCACA ACCCCAGGAG TTCCATAGCT GTCAAACTTT TTAAGTTCTC CAGGGAAAAG 180

AAAGCAGCTA AGACGTTGGG CATTGTGGTC GGTATGTTCA TCTTGTGCTG GCTACCCTTC 240

TTCATCGCTC TACCGCTTGG CTCCTTGTTC TCCACCCTGA AGCCCCCCGA CGCCGTGTTC 300

AAGGTGGTGT TCTGGCTGGG CTACTTCAAC AGCTGCCTCA ACCCCATCAT CTACCCATGC 360

TCCAGCAAGG AGTTCAAGCG CGCTTTCGT 389

(2) INFORMATION FOR SEQ ID NO:21:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 27 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

TTTGAATTCA TGTTCAAGGT GGTGTTC 27

(2) INFORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 35 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

TTTGAATTCT AAAASTGNCC NGGNSCCAGN GGCAT 35

(2) INFORMATION FOR SEQ ID NO:23:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 582 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: both
(D) TOPOLOGY: both
(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

```
GAATTCATGA TTCAAGGTGG TGTTCTGGCT GGGCTACTTC AACAGCTGCC TCAATCCCAT     60
CATCTACCCG TGCTCCAGCA AGGAGTTCAA GCGCGCCTTC ATGCGTATCC TTGGGTGCCA    120
GTGCCGCGGT GGCCGCCGCC GCCGCCGCCG TCGCCGTCTA GGCGCGTGCG CTTACACCTA    180
CCGGCCGTGG ACCCGCGGCG GCTCGCTGGA GAGATCACAG TCGCGGAAGG ACTCTCTGGA    240
TGACAGCGGC AGCTGCATGA GCGGCCAGAA GAGGACCCTG CCCTCGGCGT CGCCCAGCCC    300
GGGCTACCTG GGTCGAGGAA CGCAGCCACC CGTGGAGCTG TGCGCCTTCC CCGAGTGGAA    360
ACCCGGGGCG CTGCTCAGCT TGCCAGAGCC TCCTGGCCGC CGCGGCCGTC TCGACTCTGG    420
GCCACTCTTC ACCTTCAAGC TCCTGGGCGA TCCTGAGAGC CCGGGAACCG AAGCGACAGC    480
CAGCAACGGG GGCTGCGACA CCACGACCGA CCTGGCCAAC GGGCAGCCCG GCTTCAAGAG    540
CAACATGCCC CTGGGCCCGG GCCACTTTTA AAAGCCGAAT TC                       582
```

(2) INFORMATION FOR SEQ ID NO:24:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1567 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: both
(D) TOPOLOGY: both

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

```
TCTAGACCAT GAATCCCGAC CTGGACACCG GCCACAACAC ATCAGCACCT GCCCACTGGG     60
GAGAGTTGAA AAATGCCAAC TTCACTGGCC CCAACCAGAC CTCGAGCAAC TCCACACTGC    120
CCCAGCTGGA CATCACCAGG GCCATCTCTG TGGGCCTGGT GCTGGGCGCC TTCATCCTCT    180
TTGCCATCGT GGGCAACATC CTAGTCATCT TGTCTGTGGC CTGCAACCGG CACCTGCGGA    240
CGCCCACCAA CTACTTCATT GTCAACCTGG CCATGGCCGA CCTGCTGTTG AGCTTCACCG    300
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TCCTGCCCTT CTCAGCGGCC CTAGAGGTGC TCGGCTACTG GGTGCTGGGG CGGATCTTCT    360
GTGACATCTG GGCAGCCGTG GATGTCCTGT GCTGCACAGC GTCCATTCTG AGCCTGTGCG    420
CCATCTCCAT CGATCGCTAC ATCGGGGTGC GCTACTCTCT GCAGTATCCC ACGCTGGTCA    480
CCCGGAGGAA GGCCATCTTG GCCCTGCTCA GTGTCTGGGT CTTGTCCACC GTCATCTCCA    540
TCGGGCCTCT CCTTGGGTGG AAGGAGCCGG CACCCAACGA TGACAAGGAG TGCGGGGTCA    600
CCGAAGAACC CTTCTATGCC CTCTTCTCCT CTCTGGGCTC CTTCTACATC CCTCTGGCGG    660
TCATTCTAGT CATGTACTGC CGTGTCTATA TAGTGGCCAA GAGAACCACC AAGAACCTAG    720
AGGCAGGAGT CATGAAGGAG ATGTCCAACT CCAAGGAGCT GACCCTGAGG ATCCATTCCA    780
AGAACTTTCA CGAGGACACC CTTAGCAGTA CCAAGGCCAA GGGCCACAAC CCCAGGAGTT    840
CCATAGCTGT CAAACTTTTT AAGTTCTCCA GGGAAAAGAA AGCAGCTAAG ACGTTGGGCA    900
TTGTGGTCGG TATGTTCATC TTGTGCTGGC TACCCTTCTT CATCGCTCTA CCGCTTGGCT    960
CCTTGTTCTC CACCCTGAAG CCCCCCGACG CCGTGTTCAA GGTGGTGTTC TGGCTGGGCT   1020
ACTTCAACAG CTGCCTCAAC CCCATCATCT ACCCATGCTC CAGCAAGGAG TTCAAGCGCG   1080
CCTTCATGCG TATCCTTGGG TGCCAGTGCC GCGGTGGCCG CCGCCGCCGC CGCCGTCGCC   1140
GTCTAGGCGC GTGCGCTTAC ACCTACCGGC CGTGGACCCG CGGCGGCTCG CTGGAGAGAT   1200
CACAGTCGCG GAAGGACTCT CTGGATGACA GCGGCAGCTG CATGAGCGGC CAGAAGAGGA   1260
CCCTGCCCTC GGCGTCGCCC AGCCCGGGCT ACCTGGGTCG AGGAACGCAG CCACCCGTGG   1320
AGCTGTGCGC CTTCCCCGAG TGGAAACCCG GGGCGCTGCT CAGCTTGCCA GAGCCTCCTG   1380
GCCGCCGCGG CCGTCTCGAC TCTGGGCCAC TCTTCACCTT CAAGCTCCTG GGCGATCCTG   1440
AGAGCCCGGG AACCGAAGCG ACAGCCAGCA ACGGGGGCTG CGACACCACG ACCGACCTGG   1500
CCAACGGGCA GCCCGGCTTC AAGAGCAACA TGCCCCTGGG CCCGGGCCAC TTTTAAAAGC   1560
CGAATTC                                                             1567
```

(2) INFORMATION FOR SEQ ID NO:25:

(i) SEQUENCE CHARACTERISTICS:
  (A) LENGTH: 515 amino acids
  (B) TYPE: amino acid
  (C) STRANDEDNESS: single
  (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein
(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: N-terminal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

```
Met Asn Pro Asp Leu Asp Thr Gly His Asn Thr Ser Ala Pro Ala His
1               5                   10                  15

Trp Gly Glu Leu Lys Asn Ala Asn Phe Thr Gly Pro Asn Gln Thr Ser
            20                  25                  30

Ser Asn Ser Thr Leu Pro Gln Leu Asp Ile Thr Arg Ala Ile Ser Val
        35                  40                  45

Gly Leu Val Leu Gly Ala Phe Ile Leu Phe Ala Ile Val Gly Asn Ile
    50                  55                  60

Leu Val Ile Leu Ser Val Ala Cys Asn Arg His Leu Arg Thr Pro Thr
65                  70                  75                  80

Asn Tyr Phe Ile Val Asn Leu Ala Met Ala Asp Leu Leu Leu Ser Phe
                85                  90                  95

Thr Val Leu Pro Phe Ser Ala Ala Leu Glu Val Leu Gly Tyr Trp Val
            100                 105                 110

Leu Gly Arg Ile Phe Cys Asp Ile Trp Ala Ala Val Asp Val Leu Cys
        115                 120                 125

Cys Thr Ala Ser Ile Leu Ser Leu Cys Ala Ile Ser Ile Asp Arg Tyr
    130                 135                 140

Ile Gly Val Arg Tyr Ser Leu Gln Tyr Pro Thr Leu Val Thr Arg Arg
145                 150                 155                 160

Lys Ala Ile Leu Ala Leu Leu Ser Val Trp Val Leu Ser Thr Val Ile
                165                 170                 175

Ser Ile Gly Pro Leu Leu Gly Trp Lys Glu Pro Ala Pro Asn Asp Asp
            180                 185                 190

Lys Glu Cys Gly Val Thr Glu Glu Pro Phe Tyr Ala Leu Phe Ser Ser
        195                 200                 205

Leu Gly Ser Phe Tyr Ile Pro Leu Ala Val Ile Leu Val Met Tyr Cys
    210                 215                 220

Arg Val Tyr Ile Val Ala Lys Arg Thr Thr Lys Asn Leu Glu Ala Gly
225                 230                 235                 240

Val Met Lys Glu Met Ser Asn Ser Lys Glu Leu Thr Leu Arg Ile His
                245                 250                 255
```

```
Ser Lys Asn Phe His Glu Asp Thr Leu Ser Ser Thr Lys Ala Lys Gly
            260                 265                 270

His Asn Pro Arg Ser Ser Ile Ala Val Lys Leu Phe Lys Phe Ser Arg
        275                 280                 285

Glu Lys Lys Ala Ala Lys Thr Leu Gly Ile Val Val Gly Met Phe Ile
    290                 295                 300

Leu Cys Trp Leu Pro Phe Phe Ile Ala Leu Pro Leu Gly Ser Leu Phe
305                 310                 315                 320

Ser Thr Leu Lys Pro Pro Asp Ala Val Phe Lys Val Val Phe Trp Leu
                325                 330                 335

Gly Tyr Phe Asn Ser Cys Leu Asn Pro Ile Ile Tyr Pro Cys Ser Ser
            340                 345                 350

Lys Glu Phe Lys Arg Ala Phe Met Arg Ile Leu Gly Cys Gln Cys Arg
        355                 360                 365

Gly Gly Arg Arg Arg Arg Arg Arg Arg Arg Leu Gly Ala Cys Ala Tyr
    370                 375                 380

Thr Tyr Arg Pro Trp Thr Arg Gly Gly Ser Leu Glu Arg Ser Gln Ser
385                 390                 395                 400

Arg Lys Asp Ser Leu Asp Asp Ser Gly Ser Cys Met Ser Gly Gln Lys
                405                 410                 415

Arg Thr Leu Pro Ser Ala Ser Pro Ser Pro Gly Tyr Leu Gly Arg Gly
            420                 425                 430

Thr Gln Pro Pro Val Glu Leu Cys Ala Phe Pro Glu Trp Lys Pro Gly
        435                 440                 445

Ala Leu Leu Ser Leu Pro Glu Pro Pro Gly Arg Arg Gly Arg Leu Asp
    450                 455                 460

Ser Gly Pro Leu Phe Thr Phe Lys Leu Leu Gly Asp Pro Glu Ser Pro
465                 470                 475                 480

Gly Thr Glu Ala Thr Ala Ser Asn Gly Gly Cys Asp Thr Thr Thr Asp
                485                 490                 495

Leu Ala Asn Gly Gln Pro Gly Phe Lys Ser Asn Met Pro Leu Gly Pro
            500                 505                 510

Gly His Phe
        515
```

(2) INFORMATION FOR SEQ ID NO:26:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1987 base pairs
(B) TYPE: nucleic acid

(C) STRANDEDNESS: both
(D) TOPOLOGY: both

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

GAATTCCCTC CTAGAAGCTG GAGAGAGCAG GAGCCTTCGG TGGGGCAGCT CAAAATGTAG 60

GTAACTGCGG GCCAGGAGCA GCGCCCAGAT GCCATCGGTC CCTGCCTTTG AGCGTCGACG 120

GCTGATCTTT TGGTTTGAGG GAGAGACTGG CGCTGGAGTT TTGAATTCCG AATCATGTGC 180

AGAATCGTGA ATCTTCCCCC AGCCAGGACG AATAAGACAG CGCGGAAAAG CAGATTCTCG 240

TAATTCTGGA ATTGCATGTT GCAAGGAGTC TCCTGGATCT TCGCACCCAG CTTCGGGTAC 300

GGGAGGGAGT CCGGGTCCCG GCTAGGCCAG CCCGCAGGTG GAGAGGGTCC CCGGCAGCCC 360

CGCGCGCCCC TGGCCATGTC TTTAATGCCC TGCCCCTTCA TGTGGCCTTC TGAGGGTTCC 420

CAGGGCTGGC CAGGGTTGTC TCCCACCCGC GCGCGCCGTC TCACCCCCAG CCAAACCCAC 480

CTGGCAGGGC TCCCTCCAGA AGAGACCTTT TGATTCCCGG CTCCCGCGCT CCCGCCTCCG 540

CGCCAGCCCG GGAGGTGGCC CTGGACAGCC GGACCTCGCC CGGCCCCGGC TGGGACCATG 600

GTGTTTCTCT CGGGAAATGC TTCCGACAGC TCCAACTGCA CCCAACCGCC GGCACCGGTG 660

AACATTTCCA AGGCCATTCT GCTCGGGGTG ATCTTGGGGG GCCTCATTCT TTTCGGGGTG 720

CTGGGTAACA TCCTAGTGAT CCTCTCCGTA GCCTGTCACC GACACCTGCA CTCAGTCACG 780

CACTACTACA TCGTCAACCG CTAGTGGCGG TGGCCGACCT CCTGCTCACC TCCACGGTGC 840

TGCCCTTCTC CGCCATCTTC GAGGTCCTAG GCTACTGGGC CTTCGGCAGG GTCTTCTGCA 900

ACATCTGGGC GGCAGTGGAT GTGCTGTGCT GCACCGCGTC CATCATGGGC CTCTGCATCA 960

TCTCCATCGA CCGCTACATC GGCGTGAGCT ACCCGCTGCG CTACCCAACC ATCGTCACCC 1020

AGAGGAGGGG TCTCATGGCT CTGCTCTGCG TCTGGGCACT CTCCCTGGTC ATATCCATTG 1080

GACCCCTCTT CGGCTGGAGG CAGCCGGCCC CCGAGGACGA GACCATCTGC CAGATCAACG 1140

AGGAGCCGGG CTACGTGCTC TTCTCGGCTC TGGGCTCCTT CTACCTGCCT CTGGCCATCA 1200

TCCTGGTCAT GTACTGCCGC GTCTACGTGG TGGCCAAGAG GGAGAGCCGG GGCCTCAAGT 1260

CTGGCCTCAA GACCGACAAG TCGGACTCGG AGCAAGTGAC GCTCCGCATC CATCGGAAAA 1320

ACGCCCCGGC AGGAGGCAGC GGGATGGCCA GCGCCAAGAC CAAGACGCAC TTCTCAGTGA 1380

GGCTCCTCAA GTTCTCCCGG GAGAAGAAAG CGGCCAAAAC GCTGGGCATC GTGGTCGGCT 1440

GCTTCGTCCT CTGCTGGCTG CCTTTTTTCT TAGTCATGCC CATTGGGTCT TTCTTCCCTG 1500

ATTTCAAGCC CTCTGAAACA GTTTTTAAAA TAGTATTTTG GCTCGGATAT CTAAACAGCT 1560

GCATCAACCC CATCATATAC CCATGCTCCA GCCAAGAGTT CAAAAAGGCC TTTCAGAATG 1620

TCTTGAGAAT CCAGTGTCTC CGCAGAAAGC AGTCGCTAGT TCCAAACATG CCCTGGGCTA 1680

CACCCTGCAC CCGCCCAGCC AGGCCGTGGA AGGGCAACAC AAGGACATGG TGCGCATCCC 1740

CGTGGGATCA AGAGAGACCT TCTACAGGAT CTCCAAGACG GATGGCGTTT GTGAATGGAA 1800

ATTTTTCTCT TCCATGCCCC GTGGATCTGC CAGGATTACA GTGTCCAAAG ACCAATCCTC 1860

CTGTACCACA GCCCGGGTGA GAAGTAAAAG CTTTTTGCAG GTCTGCTGCT GTGTAGGGCC 1920

CTCAACCCCC AGCCTTGACA AGAACCATCA AGTTCCAACC ATTAAGGTCC ACACCATCTC 1980

CCTCAGT 1987

(2) INFORMATION FOR SEQ ID NO:27:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1997 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: both
(D) TOPOLOGY: both

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

AATTCCCTCC TAGAAGCTGG AGAGAGCAGG AGCCTTCGGT GGGGCAGCTC AAAATGTAGG 60

TAACTGCGGG CCAGGAGCAG CGCCCAGATG CCATCGGTCC CTGCCTTTGA GCGTCGACGG 120

CTGATCTTTT GGTTTGAGGG AGAGACTGGC GCTGGAGTTT TGAATTCCGA ATCATGTGCA 180

GAATCGTGAA TCTTCCCCCA GCCAGGACGA ATAAGACAGC GCGGAAAAGC AGATTCTCGT 240

AATTCTGGAA TTGCATGTTG CAAGGAGTCT CCTGGATCTT CGCACCCAGC TTCGGGTACG 300

GGAGGGAGTC CGGGTCCCGG CTAGGCCAGC CCGCAGGTGG AGAGGGTCCC CGGCAGCCCC 360

GCGCGCCCCT GGCCATGTCT TTAATGCCCT GCCCCTTCAT GTGGCCTTCT GAGGGTTCCC 420

AGGGCTGGCC AGGGTTGTCT CCCACCCGCG CGCGCCGTCT CACCCCCAGC CAAACCCACC 480

TGGCAGGGCT CCCTCCAGAA GAGACCTTTT GATTCCCGGC TCCCGCGCTC CCGCCTCCGC 540

GCCAGCCCGG GAGGTGGCCC TGGACAGCCG GACCTCGCCC GGCCCCGGCT GGGACCATGG 600

TGTTTCTCTC GGGAAATGCT TCCGACAGCT CCAACTGCAC CCAACCGCCG GCACCGGTGA 660

ACATTTCCAA GGCCATTCTG CTCGGGGTGA TCTTGGGGGG CCTCATTCTT TTCGGGGTGC 720

TGGGTAACAT CCTAGTGATC CTCTCCGTAG CCTGTCACCG ACACCTGCAC TCAGTCACGC 780

ACTACTACAT CGTCAACCTG GCGGTGGCCG ACCTCCTGCT CACCTCCACG GTGCTGCCCT 840

TCTCCGCCAT CTTCGAGGTC CTAGGCTACT GGGCCTTCGG CAGGGTCTTC TGCAACATCT 900

GGGCGGCAGT GGATGTGCTG TGCTGCACCG CGTCCATCAT GGGCCTCTGC ATCATCTCCA 960

TCGACCGCTA CATCGGCGTG AGCTACCCGC TGCGCTACCC AACCATCGTC ACCCAGAGGA 1020

GGGGTCTCAT GGCTCTGCTC TGCGTCTGGG CACTCTCCCT GGTCATATCC ATTGGACCCC 1080

TCTTCGGCTG GAGGCAGCCG GCCCCCGAGG ACGAGACCAT CTGCCAGATC AACGAGGAGC 1140

CGGGCTACGT GCTCTTCTCG GCTCTGGGCT CCTTCTACCT GCCTCTGGCC ATCATCCTGG 1200

TCATGTACTG CCGCGTCTAC GTGGTGGCCA AGAGGGAGAG CCGGGGCCTC AAGTCTGGCC 1260

TCAAGACCGA CAAGTCGGAC TCGGAGCAAG TGACGCTCCG CATCCATCGG AAAAACGCCC 1320

CGGCAGGAGG CAGCGGGATG GCCAGCGCCA AGACCAAGAC GCACTTCTCA GTGAGGCTCC 1380

TCAAGTTCTC CCGGGAGAAG AAAGCGGCCA AAACGCTGGG CATCGTGGTC GGCTGCTTCG 1440

TCCTCTGCTG GCTGCCTTTT TTCTTAGTCA TGCCCATTGG GTCTTTCTTC CCTGATTTCA 1500

AGCCCTCTGA AACAGTTTTT AAAATAGTAT TTTGGCTCGG ATATCTAAAC AGCTGCATCA 1560

ACCCCATCAT ATACCCATGC TCCAGCCAAG AGTTCAAAAA GGCCTTTCAG AATGTCTTGA 1620

GAATCCAGTG TCTCTGCAGA AAGCAGTCTT CCAAACATGC CCTGGGCTAC ACCCTGCACC 1680

CGCCCAGCCA GGCCGTGGAA GGGCAACACA AGGACATGGT GCGCATCCCC GTGGGATCAA 1740

GAGAGACCTT CTACAGGATC TCCAAGACGG ATGGCGTTTG TGAATGGAAA TTTTTCTCTT 1800

CCATGCCCCG TGGATCTGCC AGGATTACAG TGTCCAAAGA CCAATCCTCC TGTACCACAG 1860

CCCGGGTGAG AAGTAAAAGC TTTTTGCAGG TCTGCTGCTG TGTAGGGCCC TCAACCCCCA 1920

GCCTTGACAA GAACCATCAA GTTCCAACCA TTAAGGTCCA CACCATCTCC CTCAGTGAGA 1980

ACGGGGAGGA AGTCTAG 1997

(2) INFORMATION FOR SEQ ID NO:28:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 466 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(iii) HYPOTHETICAL: NO

(v) FRAGMENT TYPE: N-terminal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

```
Met Val Phe Leu Ser Gly Asn Ala Ser Asp Ser Ser Asn Cys Thr Gln
1               5                   10                  15

Pro Pro Ala Pro Val Asn Ile Ser Lys Ala Ile Leu Leu Gly Val Ile
            20                  25                  30

Leu Gly Gly Leu Ile Leu Phe Gly Val Leu Gly Asn Ile Leu Val Ile
        35                  40                  45

Leu Ser Val Ala Cys His Arg His Leu His Ser Val Thr His Tyr Tyr
    50                  55                  60

Ile Val Asn Leu Ala Val Ala Asp Leu Leu Leu Thr Ser Thr Val Leu
65                  70                  75                  80

Pro Phe Ser Ala Ile Phe Glu Val Leu Gly Tyr Trp Ala Phe Gly Arg
                85                  90                  95

Val Phe Cys Asn Ile Trp Ala Ala Val Asp Val Leu Cys Cys Thr Ala
            100                 105                 110

Ser Ile Met Gly Leu Cys Ile Ile Ser Ile Asp Arg Tyr Ile Gly Val
        115                 120                 125

Ser Tyr Pro Leu Arg Tyr Pro Thr Ile Val Thr Gln Arg Arg Gly Leu
    130                 135                 140

Met Ala Leu Leu Cys Val Trp Ala Leu Ser Leu Val Ile Ser Ile Gly
145                 150                 155                 160

Pro Leu Phe Gly Trp Arg Gln Pro Ala Pro Glu Asp Glu Thr Ile Cys
                165                 170                 175

Gln Ile Asn Glu Glu Pro Gly Tyr Val Leu Phe Ser Ala Leu Gly Ser
            180                 185                 190

Phe Tyr Leu Pro Leu Ala Ile Ile Leu Val Met Tyr Cys Arg Val Tyr
        195                 200                 205
```

Val Val Ala Lys Arg Glu Ser Arg Gly Leu Lys Ser Gly Leu Lys Thr
210 215 220

Asp Lys Ser Asp Ser Glu Gln Val Thr Leu Arg Ile His Arg Lys Asn
225 230 235 240

Ala Pro Ala Gly Gly Ser Gly Met Ala Ser Ala Lys Thr Lys Thr His
245 250 255

Phe Ser Val Arg Leu Leu Lys Phe Ser Arg Glu Lys Lys Ala Ala Lys
260 265 270

Thr Leu Gly Ile Val Val Gly Cys Phe Val Leu Cys Trp Leu Pro Phe
275 280 285

Phe Leu Val Met Pro Ile Gly Ser Phe Phe Pro Asp Phe Lys Pro Ser
290 295 300

Glu Thr Val Phe Lys Ile Val Phe Trp Leu Gly Tyr Leu Asn Ser Cys
305 310 315 320

Ile Asn Pro Ile Ile Tyr Pro Cys Ser Ser Gln Glu Phe Lys Lys Ala
325 330 335

Phe Gln Asn Val Leu Arg Ile Gln Cys Leu Cys Arg Lys Gln Ser Ser
340 345 350

Lys His Ala Leu Gly Tyr Thr Leu His Pro Pro Ser Gln Ala Val Glu
355 360 365

Gly Gln His Lys Asp Met Val Arg Ile Pro Val Gly Ser Arg Glu Thr
370 375 380

Phe Tyr Arg Ile Ser Lys Thr Asp Gly Val Cys Glu Trp Lys Phe Phe
385 390 395 400

Ser Ser Met Pro Arg Gly Ser Ala Arg Ile Thr Val Ser Lys Asp Gln
405 410 415

Ser Ser Cys Thr Thr Ala Arg Val Arg Ser Lys Ser Phe Leu Gln Val
420 425 430

Cys Cys Cys Val Gly Pro Ser Thr Pro Ser Leu Asp Lys Asn His Gln
435 440 445

Val Pro Thr Ile Lys Val His Thr Ile Ser Leu Ser Glu Asn Gly Glu
450 455 460

Glu Val
465

(2) INFORMATION FOR SEQ ID NO:29:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1776 base pairs
(B) TYPE: nucleic acid

(C) STRANDEDNESS: both
(D) TOPOLOGY: both

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

```
CTCCCTGCCG GCCGCTCGTT CTGTGCCCCG GCCCGGCCAC CGACGGCCGG CGTTGAGATG     60
ACTTTCCGCG ATCTCCTGAG CGTCAGTTTC GAGGGACCCC GCCCGGACAG CAGCGCAGGG    120
GGCTCCAGCG CGGGCGGCGG CGGGGGCGGC GCGGGCGGCG CGGCCCCCTC GGAGGGCCCG    180
GCGGTGGGCG GCGTGCCGGG GGGCGCGGGC GGCGGCGGCG GCGTGGTGGG CGCAGGCAGC    240
GGCGAGGACA ACCGGAGCTC CGCGGGGGAG CCGGGGAGCG CGGGCGCGGG CGGCGACGTG    300
AATGGCACGG CGGCCGTCGG GGGACTGGTG GTGAGCGCGC AGGGCGTGGG CGTGGGCGTC    360
TTCCTGGCAG CCTTCATCCT TATGGCCGTG GCAGGTAACC TGCTTGTCAT CCTCTCAGTG    420
GCCTGCAACC GCCACCTGCA GACCGTCACC AACTATTTCA TCGTGAACCT GGCCGTGGCC    480
GACCTGCTGC TGAGCGCCAC CGTACTGCCC TTCTCGGCCA CCATGGAGGT TCTGGGCTTC    540
TGGGCCTTTG GCCGCGCCTT CTGCGACGTA TGGGCCGCCG TGGACGTGCT GTGCTGCACG    600
GCCTCCATCC TCAGCCTCTG CACCATCTCC GTGGACCGGT ACGTGGGCGT GCGCCACTCA    660
CTCAAGTACC CAGCCATCAT GACCGAGCGC AAGGCGGCCG CCATCCTGGC CCTGCTCTGG    720
GTCGTAGCCC TGGTGGTGTC CGTAGGGCCC CTGCTGGGCT GGAAGGAGCC CGTGCCCCCT    780
GACGAGCGCT TCTGCGGTAT CACCGAGGAG GCGGGCTACG CTGTCTTCTC CTCCGTGTGC    840
TCCTTCTACC TGCCCATGGC GGTCATCGTG GTCATGTACT GCCGCGTGTA CGTGGTCGCG    900
CGCAGCACCA CGCGCAGCCT CGAGGCGGGC GTCAAGCGCG AGCGAGGCAA GGCCTCCGAG    960
GTGGTGCTGC GCATCCACTG TCGCGGCGCG GCCACGGGCG CCGACGGGGC GCACGGCATG   1020
CGCAGCGCCA AGGGCCACAC CTTCCGCAGC TCGCTCTCCG TGCGCCTGCT CAAGTTCTCC   1080
CGTGAGAAGA AAGCGGCCAA GACTCTGGCC ATCGTCGTGG GTGTCTTCGT GCTCTGCTGG   1140
TTCCCTTTCT TCTTTGTCCT GCCGCTCGGC TCCTTGTTCC CGCAGCTGAA GCCATCGGAG   1200
GGCGTCTTCA AGGTCATCTT CTGGCTCGGC TACTTCAACA GCTGCGTGAA CCCGCTCATC   1260
TACCCCTGTT CCAGCCGCGA GTTCAAGCGC GCCTTCCTCC GTCTCCTGCG CTGCCAGTGC   1320
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CGTCGTCGCC GGCGCCGCCG CCCTCTCTGG CGTGTCTACG GCCACCACTG GCGGGCCTCC 1380

ACCAGCGGCC TGCGCCAGGA CTGCGCCCCG AGTTCGGGCG ACGCGCCCCC CGGAGCGCCG 1440

CTGGCCCTCA CCGCGCTCCC CGACCCCGAC CCCGAACCCC CAGGCACGCC CGAGATGCAG 1500

GCTCCGGTCG CCAGCCGTCG AAAGCCACCC AGCGCCTTCC GCGAGTGGAG GCTGCTGGGG 1560

CCGTTCCGGA GACCCACGAC CCAGCTGCGC GCCAAAGTCT CCAGCCTGTC GCACAAGATC 1620

CGCGCCGGGG GCGCGCAGCG CGCAGAGGCA GCGTGCGCCC AGCGCTCAGA GGTGGAGGCT 1680

GTGTCCCTAG GCGTCCCACA CGAGGTGGCC GAGGGCGCCA CCTGCCAGGC CTACGAATTG 1740

GCCGACTACA GCAACCTACG GGAGACCGAT ATTTAA 1776

(2) INFORMATION FOR SEQ ID NO:30:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 572 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(v) FRAGMENT TYPE: N-terminal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

Met Thr Phe Arg Asp Leu Leu Ser Val Ser Phe Glu Gly Pro Arg Pro
1 5 10 15

Asp Ser Ser Ala Gly Gly Ser Ser Ala Gly Gly Gly Gly Gly Gly Ala
20 25 30

Gly Gly Ala Ala Pro Ser Glu Gly Pro Ala Val Gly Gly Val Pro Gly
35 40 45

Gly Ala Gly Gly Gly Gly Gly Val Val Gly Ala Gly Ser Gly Glu Asp
50 55 60

Asn Arg Ser Ser Ala Gly Glu Pro Gly Ser Ala Gly Ala Gly Gly Asp
65 70 75 80

Val Asn Gly Thr Ala Ala Val Gly Gly Leu Val Val Ser Ala Gln Gly
85 90 95

Val Gly Val Gly Val Phe Leu Ala Ala Phe Ile Leu Met Ala Val Ala

```
                100                       105                       110

Gly Asn Leu Leu Val Ile Leu Ser Val Ala Cys Asn Arg His Leu Gln
        115                     120                     125

Thr Val Thr Asn Tyr Phe Ile Val Asn Leu Ala Val Ala Asp Leu Leu
    130                     135                     140

Leu Ser Ala Thr Val Leu Pro Phe Ser Ala Thr Met Glu Val Leu Gly
145                     150                     155                     160

Phe Trp Ala Phe Gly Arg Ala Phe Cys Asp Val Trp Ala Ala Val Asp
                165                     170                     175

Val Leu Cys Cys Thr Ala Ser Ile Leu Ser Leu Cys Thr Ile Ser Val
            180                     185                     190

Asp Arg Tyr Val Gly Val Arg His Ser Leu Lys Tyr Pro Ala Ile Met
        195                     200                     205

Thr Glu Arg Lys Ala Ala Ala Ile Leu Ala Leu Leu Trp Val Val Ala
    210                     215                     220

Leu Val Val Ser Val Gly Pro Leu Leu Gly Trp Lys Glu Pro Val Pro
225                     230                     235                     240

Pro Asp Glu Arg Phe Cys Gly Ile Thr Glu Glu Ala Gly Tyr Ala Val
                245                     250                     255

Phe Ser Ser Val Cys Ser Phe Tyr Leu Pro Met Ala Val Ile Val Val
            260                     265                     270

Met Tyr Cys Arg Val Tyr Val Val Ala Arg Ser Thr Thr Arg Ser Leu
        275                     280                     285

Glu Ala Gly Val Lys Arg Glu Arg Gly Lys Ala Ser Glu Val Val Leu
    290                     295                     300

Arg Ile His Cys Arg Gly Ala Ala Thr Gly Ala Asp Gly Ala His Gly
305                     310                     315                     320

Met Arg Ser Ala Lys Gly His Thr Phe Arg Ser Ser Leu Ser Val Arg
                325                     330                     335

Leu Leu Lys Phe Ser Arg Glu Lys Lys Ala Ala Lys Thr Leu Ala Ile
            340                     345                     350

Val Val Gly Val Phe Val Leu Cys Trp Phe Pro Phe Phe Phe Val Leu
        355                     360                     365

Pro Leu Gly Ser Leu Phe Pro Gln Leu Lys Pro Ser Glu Gly Val Phe
    370                     375                     380

Lys Val Ile Phe Trp Leu Gly Tyr Phe Asn Ser Cys Val Asn Pro Leu
385                     390                     395                     400
```

Ile Tyr Pro Cys Ser Ser Arg Glu Phe Lys Arg Ala Phe Leu Arg Leu
405 410 415

Leu Arg Cys Gln Cys Arg Arg Arg Arg Arg Arg Arg Pro Leu Trp Arg
420 425 430

Val Tyr Gly His His Trp Arg Ala Ser Thr Ser Gly Leu Arg Gln Asp
435 440 445

Cys Ala Pro Ser Ser Gly Asp Ala Pro Pro Gly Ala Pro Leu Ala Leu
450 455 460

Thr Ala Leu Pro Asp Pro Asp Pro Glu Pro Pro Gly Thr Pro Glu Met
465 470 475 480

Gln Ala Pro Val Ala Ser Arg Arg Lys Pro Pro Ser Ala Phe Arg Glu
485 490 495

Trp Arg Leu Leu Gly Pro Phe Arg Arg Pro Thr Thr Gln Leu Arg Ala
500 505 510

Lys Val Ser Ser Leu Ser His Lys Ile Arg Ala Gly Gly Ala Gln Arg
515 520 525

Ala Glu Ala Ala Cys Ala Gln Arg Ser Glu Val Glu Ala Val Ser Leu
530 535 540

Gly Val Pro His Glu Val Ala Glu Gly Ala Thr Cys Gln Ala Tyr Glu
545 550 555 560

Leu Ala Asp Tyr Ser Asn Leu Arg Glu Thr Asp Ile
565 570

(2) INFORMATION FOR SEQ ID NO:31:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: both
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:

GAATCCCGAC CTGGAC 16

(2) INFORMATION FOR SEQ ID NO:32:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: both
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:

GGATCCTCAG GGTC 14

(2) INFORMATION FOR SEQ ID NO:33:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: both
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:

CCATGGTGTT TCTCTCGGG 19

(2) INFORMATION FOR SEQ ID NO:34:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: both
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:34:

GACGCGGCAG TACATGAC 18

(2) INFORMATION FOR SEQ ID NO:35:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: both
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

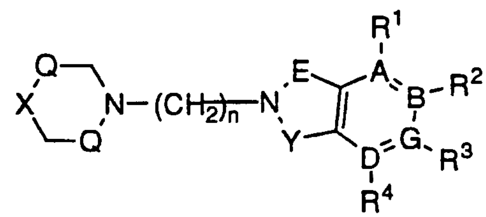
(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:35:

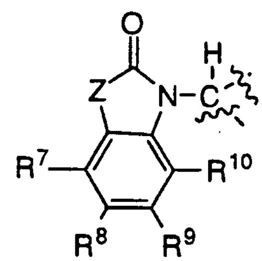
GTCATGATGG CTGGGTACTT G 21

WHAT IS CLAIMED IS:

1. A compound having the formula:

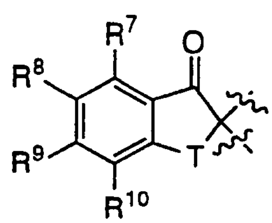


and a pharmaceutically acceptable salt, prodrug, polymorph, or metabolite thereof wherein:
n is an integer from 3 to 5;
Y represents carbonyl, sulphonyl, $-CO-CH_2-$, or $-CO-NR^{12}-$;
R^{12} is hydrogen, substituted or unsubstituted lower alkyl, substituted or unsubstituted phenyl;
E is carbonyl or sulphonyl;
A, B, G, D are independently carbon or nitrogen;
R^1-R^4 are independently selected from the group consisting of hydrogen; halogen; nitro; amino; substituted or unsubstituted lower alkyl; perhalogenated lower alkyl; substituted or unsubstituted lower alkoxy; sulfonyl alkyl; and substituted or unsubstituted aryl or heteroaryl, with the proviso that if any of A, B, G, or D is a nitrogen, then the substituent R group is not present;
Q is, independently, $(-CH_2-)_r$, -NH-, S, or O;
r is 0-3; and
X is
a)



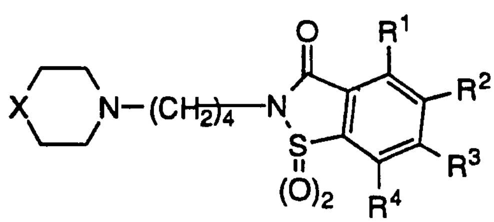
, or

b)



T is nitrogen, carbon, lower alkylene of one to three carbons or lower alkenylene of one to three carbons;
R^7-R^{10} are independently selected from the group consisting of hydrogen, lower alkyl, lower alkenyl, and lower alkoxy; and
Z is O, S, CH_2, CH_2O, OCH_2, SCH_2, lower alkylene, lower alkenylene, NH, or NMe.

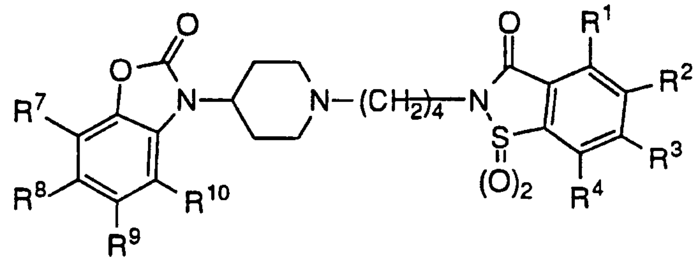
2. The compound of Claim 1 having the structure:



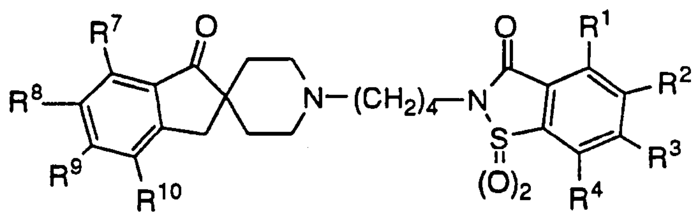
and a pharmaceutically acceptable salt, prodrug, polymorph, or metabolite thereof wherein all substituents are as defined in Claim 1.

3. The compound of Claim 2 which is a benzoxazolinyl piperidine substituted butyl saccharine or a spiro 1-oxo-2H-indenenyl piperidine substituted butyl saccharine.

4. The compound of Claim 3 selected from:



and



wherein all substituents are as defined in Claim 1.

5. A compound selected from:
1,1-Dioxido-2-(4-(4-(2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one;
1,1-Dioxido-2-(4-(4-(3,4-dihydro-2-oxo-(1*H*)-quinolin-1-yl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one;
1,1-Dioxido-2-(4-(4-(2-oxo-3,1,4-benzoxazinyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one;
1,1-Dioxido-2-(4-(4-(2-oxo-(1H)-quinolin-1-yl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one;
1,1-Dioxido-2-(4-(4-(2-oxo-(1H)-quinolin-1-yl)-piperidin-1-yl)-butyl)-5-nitro-1,2-benzisothiazol-3(2H)-one;

6-Chloro-1,1-dioxido-2-(4-(4-(2-oxo-(1H)-quinolin-1-yl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one;
5-Chloro-1,1-dioxido-2-(4-(4-(2-oxo-(1H)-quinolin-1-yl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one;
1,1-Dioxido-2-(4-(4-(2-oxo-(1H)-quinolin-1-yl)-piperidin-1-yl)-butyl)-7-nitro-1,2-benzisothiazol-3(2H)-one;
1,1-Dioxido-2-(4-(4-(2-oxo-(1H)-quinolin-1-yl)-piperidin-1-yl)-butyl)-4-methoxy-1,2-benzisothiazol-3(2H)-one;
1,1-Dioxido-2-(4-(4-(2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-5-nitro-1,2-benzisothiazol-3(2H)-one;
6-Chloro-1,1-dioxido-2-(4-(4-(2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one;
5-Chloro-1,1-dioxido-2-(4-(4-(2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one;
1,1-Dioxido-2-(4-(4-(2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-7-nitro-1,2-benzisothiazol-3(2H)-one;
1,1-Dioxido-2-(4-(4-(2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-4-methoxy-1,2-benzisothiazol-3(2H)-one;
1,1-Dioxido-2-(4-(4-(5-chloro-2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one;
1,1-Dioxido-2-(4-(4-(3a-(*R*)-8a-(*S*)-2-oxo-3,3a,8,8a-tetrahydro-2H-indeno[1,2-d]oxazolinyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one;
1,1-Dioxido-2-(4-(4-(2-oxonaphth[2,3-d]oxazolinyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one;
1,1-Dioxido-2-(4-(4-(6-methyl-2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one;
1,1-Dioxido-2-(4-(4-(2-oxo-5-phenyl-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one;
1,1-Dioxido-2-(4-(4-(6-methoxy-2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one;
1,1-Dioxido-2-(4-(4-(6-carbomethoxy-2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one;

1,1-Dioxido-2-(4-(4-(5-ethylsulfonyl-2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one;
1,1-Dioxido-2-(4-(4-(2-oxo-3-oxazolo[4,5-b]pyridyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one;
1,1-Dioxido-2-(4-(4-(7-carbethoxy-2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one;
1,1-Dioxido-2-(4-(4-(5-*tert*-butyl-2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one;
1,1-Dioxido-2-(4-(4-(5,7-dimethyl-2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one;
1,1-Dioxido-2-(4-(spiro(1,3-dihydro-1-oxo-2H-indene-2,4'-piperidin-1'-yl)butyl)-1,2-benzisothiazol-3(2H)-one;
1,1-Dioxido-2-(4-(4'-(3,4-dihydro-1-oxonapththalene)-2(1H)-spiropiperidin-1'-yl)butyl)-1,2-benzisothiazol-3(2H)-one;
4-(3,4-Dihydro-6-methyl-spiro[2H-1-benzopyran-2,4'-piperidine-4(3H)-one]-1'-yl)-butylphthalimide;
4-(Spiro(piperidine-4,6'-[6H]thieno[2,3-b]thiopyran-4'(5'H)-one-1'-yl)-butylphthalimide;
4-(Spiro[benzothiazol-2(3H),4'-piperidin-1'-yl)-butylphthalimide;
4-(3,4-Dihydro-6-methoxy-spiro[2H-1-benzopyran-2,4'-piperidine-4(3H)-one]-1'-yl)-butylphthalimide;
4-(3,4-Dihydro-6-methanesulfonylamidyl-spiro[2H-1-benzopyran-2,4'-piperidine-4(3H)-one]-1'-yl)-butylphthalimide;
1,1-Dioxido-2-(4-(spiro[benzothiazol-2(3H),4'-piperidin-1'-yl)-butyl)-1,2-benzisothiazol-3(2H)-one;
4-(6-Trifluoromethyl-spiro[benzothiazol-2(3H),4'-piperidin-1'-yl)-butylphthalimide;
1,1-Dioxido-2-(4-(spiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-butyl)-1,2-benzisothiazol-3(2H)-one;
4-(Spiro[benzofuran-2(3H),4'-piperidin]-1'-yl)-butylphthalimide;
4-(Spiro[2H-1,3-benzoxazine-2,4'-piperidin]-1'-yl)-butylphthalimide;
3,3-Dioxido-1,2-dehydro-2-(4-(spiro[2H-indene-2,4'-piperidine-1(3H)-one]-1'-yl)-butyl)-naphth[1,2-d]isothiazol-1-one;

1,1-Dioxido-2-(4-(spiro[2H-indene-2,4'-piperidine-1(3H)-one]-1'-yl)-butyl)-4-methoxy-1,2-benzisothiazol-3(2H)-one;
1,1-Dioxido-2-(4-(spiro[2H-indene-2,4'-piperidine-1(3H)-one]-1'-yl)-butyl)-7-methoxy-1,2-benzisothiazol-3(2H)-one;
1,1-Dioxido-2-(4-(spiro(1,3-dihydro-1-oxo-2H-indene-2,4'-piperidin-1'-yl)butyl)-5-methoxy-1,2-benzisothiazol-3(2H)-one;
1,1-Dioxido-2-(4-(spiro(1,3-dihydro-1-oxo-2H-indene-2,4'-piperidin-1'-yl)butyl)-6-methoxy-1,2-benzisothiazol-3(2H)-one;
1,1-Dioxido-2-(4-(spiro(1,3-dihydro-1-oxo-2H-indene-2,4'-piperidin-1'-yl)butyl)-5-methyl-1,2-benzisothiazol-3(2H)-one;
1,1-Dioxido-2-(4-(spiro(1,3-dihydro-1-oxo-2H-indene-2,4'-piperidin-1'-yl)butyl)-5-chloro-1,2-benzisothiazol-3(2H)-one;
1,1-Dioxido-2-(4-(spiro(1,3-dihydro-1-oxo-2H-indene-2,4'-piperidin-1'-yl)butyl)-5-fluoro-1,2-benzisothiazol-3(2H)-one;
1,1-Dioxido-2-(4-(spiro(1,3-dihydro-1-oxo-2H-indene-2,4'-piperidin-1'-yl)butyl)-5-nitro-1,2-benzisothiazol-3(2H)-one;
1,1-Dioxido-2-(4-(spiro(1,3-dihydro-1-oxo-2H-indene-2,4'-piperidin-1'-yl)butyl)-6-nitro-1,2-benzisothiazol-3(2H)-one;
1,1-Dioxido-2-(4-(spiro(1,3-dihydro-1-oxo-2H-indene-2,4'-piperidin-1'-yl)butyl)-isothiazolo[5,4-c]pyridin-3(2H)-one;
1,1-Dioxido-2-(4-(spiro(1,3-dihydro-1-oxo-2H-indene-2,4'-piperidin-1'-yl)butyl)-isothiazolo[5,4-b]pyridin-3(2H)-one ;
1,1-Dioxido-2-(4-(4-(6-methyl-2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-5-nitro-1,2-benzisothiazol-3(2H)-one;
2-(4-(Spiro(1,3-dihydro-1-oxo-2H-indene-2,4'-piperidin-1'-yl)butyl)-pyrrolo[3,4b]pyridin-5,7(1H)-dione;
1,1-Dioxido-2,3-dihydro-2-(4-(spiro[2H-indene-2,4'-piperidine-1(3H)-one]-1'-yl)-butyl)-naphth[1,8-de]isothiazin-3-one; and
1,1-Dioxido-2-(4-(spiro[3-oxo-phthalan-1,4'-piperidin-1'-yl)butyl)-1,2-benzisothiazol-3(2H)-one;
1,1-Dioxido-2-(4-(4-(1,3-dihydro-2-oxo-2H-benzimidazolin-1-yl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one;
1,1-Dioxido-2-(4-(4-(1,3-dihydro-2-oxo-3-methyl-2H-benzimidazolin-1-yl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one;

1,1-Dioxido-2-(4-(4-(1,3-dihydro-2-oxo-5-methyl-2H-benzimidazolin-1-yl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one;
1,1-Dioxido-2-(4-(4-(1,3-dihydro-2-oxo-4-methyl-2H-benzimidazolin-1-yl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one;
1,1-Dioxido-2-(4-(4-(1,3-dihydro-2-oxo-5-methoxy-2H-benzimidazolin-1-yl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one;
1,1-Dioxido-2-(4-(4-(1,3-dihydro-2-oxo-5-chloro-2H-benzimidazolin-1-yl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one;
1,1-Dioxido-2-(4-(4-(1,3-dihydro-2-oxo-5-fluoro-2H-benzimidazolin-1-yl)-piperidin-1-yl)-butyl)-5-chloro-1,2-benzisothiazol-3(2H)-one;
1,1-Dioxido-2-(4-(4-(1,3-dihydro-2-oxo-5-methyl-2H-benzimidazolin-1-yl)-piperidin-1-yl)-butyl)-5-chloro-1,2-benzisothiazol-3(2H)-one;
1,1-Dioxido-2-(4-(4-(1,3-dihydro-2-oxo-6-methyl-2H-benzimidazolin-1-yl)-piperidin-1-yl)-butyl)-5-chloro-1,2-benzisothiazol-3(2H)-one;
1,1-Dioxido-2-(4-(4-(5-methyl-2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-5,6-dihydro-[1,4]dioxino[2,3-e]benzisothiazol-3(2H)-one;
1,1-Dioxido-2-(4-(4-(2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-5,6-dihydro-[1,4]dioxino[2,3-e]benzisothiazol-3(2H)-one;
1,1-Dioxido-2-(4-(4-(spiro-1,3-dihydro-1-oxo-2H-indenyl)-2,4'-piperidin-1'-yl)-butyl)-5,6-dihydro-[1,4]dioxino[2,3-e]benzisothiazol-3(2H)-one;
1,1-Dioxido-2-(4-(4-(1,3-dihydro-2-oxo-1H-3,4-dihydroquinazolin-1-yl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one;
2-(4-Hydroxybutyl)-1,1-dioxido-5,6-dihydro-[1,4]dioxino[2,3-d]benzisothiazol-3(2H)-one;
1,1-Dioxido-2-(4-(4-(2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-5-ethoxy-1,2-benzothiazol-3(2H)-one;
1,1-Dioxido-2-(4-(4-(spiro-1,3-dihydro-1-oxo-2H-indenyl)-2,4'-piperidin-1'-yl)-butyl)-5-ethoxy-1,2-benzothiazol-3(2H)-one;
1,1-Dioxido-2-(4-(4-(spiro-1,3-dihydro-1-oxo-2H-indenyl)-2,4'-piperidin-1'-yl)-butyl)-5-ethyl-1,2-benzothiazol-3(2H)-one;
1,1-Dioxido-2-(4-(4-(2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-5-ethyl-1,2-benzothiazol-3(2H)-one;

1,1-Dioxido-2-(4-(4-(spiro-1,3-dihydro-1-oxo-2H-indenyl)-2,4'-piperidin-1'-yl)-butyl)-5-(2-propyl)-1,2-benzothiazol-3(2H)-one;
1,1-Dioxido-2-(4-(4-(2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-5-(2-propyl)-1,2-benzothiazol-3(2H)-one;
1,1-Dioxido-2-(4-(4-(2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-6-nitro-1,2-benzisothiazol-3(2H)-one;
1,1-Dioxido-2-(4-(4-(2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-5-fluoro-1,2-benzisothiazol-3(2H)-one;
1,1-Dioxido-2-(4-(4-(2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-5-methyl-1,2-benzisothiazol-3(2H)-one;
1,1-Dioxido-2-(4-(4-(2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-5-bromo-1,2-benzisothiazol-3(2H)-one;
1,1-Dioxido-2-(4-(4-(2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-5-trifluoromethyl-1,2-benzisothiazol-3(2H)-one;
1,1-Dioxido-2-(4-(4-(2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-5-trifluoromethoxy-1,2-benzisothiazol-3(2H)-one;
1,1-Dioxido-2-(4-(4-(2-oxo-1-naphth[1,2-d]oxazolinyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one;
1,1-Dioxido-2-(4-(4-(5,6,7,8-tetrahydro-2-oxo-3-naphth[2,3-d]oxazolinyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one;
1,1-Dioxido-2-(4-(4-(5-methyl-2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one;
1,1-Dioxido-2-(4-(4-(5-carbomethoxy-2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one;
1,1-Dioxido-2-(4-(4-(6-fluoro-2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one;
1,1-Dioxido-2-(4-(4-(4-methyl-2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one;
1,1-Dioxido-2-(4-(4-(4-methoxy-2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one;
5-Chloro-1,1-dioxido-2-(4-(4-(6-methyl-2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one;
5-Methylthio-1,1-dioxido-2-(4-(4-(6-methyl-2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one;

5-Ethoxy-1,1-dioxido-2-(4-(4-(6-methyl-2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one;
5-Chloro-1,1-dioxido-2-(4-(4-(6-fluoro-2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one;
4-Methyl-1,1-dioxido-2-(4-(4-(2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one;
4-Chloro-1,1-dioxido-2-(4-(4-(2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one;
4-Ethoxy-1,1-dioxido-2-(4-(4-(2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one;
4-(2-Propyloxy)-1,1-dioxido-2-(4-(4-(2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one;
5-Methoxy-1,1-dioxido-2-(4-(4-(6-methyl-2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one;
1,1-Dioxido-2-(4-(4-(2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-6-methylsulfonyl-1,2-benzisothiazol-3(2H)-one;
5-Methoxy-1,1-dioxido-2-(4-(4-(2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one;
1,1-Dioxido-2-(4-(4-(2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-5-methylsulfonyl-1,2-benzisothiazol-3(2H)-one;
5-Methylthio-1,1-dioxido-2-(4-(4-(2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one;
5-Methylsulfonyl-1,1-dioxido-2-(4-(4-(6-methyl-2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one; or
1,1-Dioxido-2-(4-(4-(2-oxo-1-oxazolo[5,4-b]pyridyl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one;
and a pharmaceutically acceptable salt, prodrug, polymorph, or metabolite thereof.

6. The compound of Claim 5 selected from:
1,1-Dioxido-2-(4-(4-(1,3-dihydro-2-oxo-2H-benzimidazolin-1-yl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one;
1,1-Dioxido-2-(4-(4-(1,3-dihydro-2-oxo-3-methyl-2H-benzimidazolin-1-yl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one;

1,1-Dioxido-2-(4-(4-(1,3-dihydro-2-oxo-5-methyl-2H-benzimidazolin-1-yl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one;
1,1-Dioxido-2-(4-(4-(1,3-dihydro-2-oxo-5-chloro-2H-benzimidazolin-1-yl)-piperidin-1-yl)-butyl)-1,2-benzisothiazol-3(2H)-one;
1,1-Dioxido-2-(4-(4-(1,3-dihydro-2-oxo-5-fluoro-2H-benzimidazolin-1-yl)-piperidin-1-yl)-butyl)-5-chloro-1,2-benzisothiazol-3(2H)-one;
1,1-Dioxido-2-(4-(4-(1,3-dihydro-2-oxo-5-methyl-2H-benzimidazolin-1-yl)-piperidin-1-yl)-butyl)-5-chloro-1,2-benzisothiazol-3(2H)-one;
1,1-Dioxido-2-(4-(4-(1,3-dihydro-2-oxo-6-methyl-2H-benzimidazolin-1-yl)-piperidin-1-yl)-butyl)-5-chloro-1,2-benzisothiazol-3(2H)-one; or
1,1-Dioxido-2-(4-(4-(5-methyl-2-oxo-3-benzoxazolinyl)-piperidin-1-yl)-butyl)-5,6-dihydro-[1,4]dioxino[2,3-e]benzisothiazol-3(2H)-one;
and a pharmaceutically acceptable salt, prodrug, polymorph, or metabolite thereof.

7. A pharmaceutical composition comprising a therapeutically effective amount of the compound of Claim 1 and a pharmaceutically acceptable carrier.

8. The composition of Claim 7 which further comprises a therapeutically effective amount of a testosterone 5-alpha reductase inhibitor.

9. The composition of Claim 8, wherein the testosterone 5-alpha reductase inhibitor is a type 1, a type 2, a type 1 and a type 2 or a dual type 1 and type 2 testosterone 5-alpha reductase inhibitor.

10. The composition of Claim 9, wherein the testosterone 5-alpha reductase inhibitor is a type 2 testosterone 5-alpha reductase inhibitor.

11. The composition of Claim 10, wherein the testosterone 5-alpha reductase inhibitor is finasteride.

12. A method of treating benign prostatic hyperplasia in a subject in need thereof which comprises administering to the subject a therapeutically effective amount of the compound of Claim 1.

13. The method of Claim 12 wherein the compound is administered in combination with a therapeutically effective amount of a testosterone 5-alpha reductase inhibitor.

14. The method of Claim 13, wherein the testosterone 5-alpha reductase inhibitor is finasteride.

15. The method of Claim 12, wherein the compound additionally does not cause a fall in blood pressure at dosages effective for treating benign prostatic hyperplasia.

16. A method of treating benign prostatic hyperplasia which comprises administering a therapeutically effective amount of the composition of claim 7.

17 A method of inhibiting contraction of prostate tissue in a subject in need thereof which comprises administering to the subject a therapeutically effective amount of the compound of Claim 1.

18. The method of Claim 17 wherein the compound is administered in combination with a therapeutically effective amount of a testosterone 5-alpha reductase inhibitor.

19. The method of Claim 18, wherein the testosterone 5-alpha reductase inhibitor is finasteride.

20. The method of Claim 17, wherein the compound additionally does not cause a fall in blood pressure at dosages effective for treating benign prostatic hyperplasia.

21. A method of using the compound of Claim 1 to selectively antagonize the human alpha1C adrenergic receptor which comprises exposing the human alpha1C adrenergic receptor to an antagonistically effective amount of said compound.

22. A method of preparing an antagonist of the human alpha1C adrenergic receptor which comprises alkylating a halogenated butyl saccharine with a deprotected spiropiperidine or a deprotected benzoxazolinyl piperidine

23. The use of the compound of Claim 1 in the preparation of a medicament for the treatment of benign prostatic hyperplasia.

24. The use of the compound of Claim 1 in the preparation of a medicament for inhibiting contraction of prostate tissue.

25. A drug which is useful for treating benign prostatic hyperplasia, the effective ingredient of the said drug being a compound as claimed in Claim 1.

26. A drug which is useful for inhibiting contraction of prostate tissue, the effective ingredient of the said drug being a compound as claimed in Claim 1.

```
  1 GCCGCGTCTA CGTGGTGGCC AAGAGGGAGA GCCGGGGCCT CAAGTCTGGC CTCAAGACCG  60

 61 ACAAGTCGGA CTCGGAGCAA GTGACGCTCC GCATCCATCG GAAAAACGCC CCGGCAGGAG 120

121 GCAGCGGGAT GGCCAGCGCC AAGACCAAGA CGCACTTCTC AGTGAGGCTC CTCAAGTTCT 180

181 CCCGGGAGAA GAAAGCGGCC AAAACGCTGG GCATCGTGGT CGGCTGCTTC GTCCT      235
```

FIG.1

```
h α1c: .......................Arg Val Tyr Val Val Ala Lys Arg Glu Ser
                               |   |   |   |   |   |   |   |   |   |
b α1c: ...Leu Val Met Tyr Cys Arg Val Tyr Val Val Ala Lys Arg Glu Ser

h α1C: ...Arg Gly Leu Lys Ser Gly Leu Lys Thr Asp Lys Ser Asp Ser Glu Gln
           |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
b α1C: ...Arg Gly Leu Lys Ser Gly Leu Lys Thr Asp Lys Ser Asp Ser Glu Gln

h α1C: ...Val Thr Leu Arg Ile His Arg Lys Asn Ala Pro Ala Gly Gly Ser Gly
           |   |   |   |   |   |   |   |   |   |   •   •   |   |   |   |
b α1C: ...Val Thr Leu Arg Ile His Arg Lys Asn Ala Gln Val Gly Gly Ser Gly

h α1c: ...Met Ala Ser Ala Lys Thr Lys Thr His Phe Ser Val Arg Leu Leu Lys
           •   •   |   |   |   •   |   |   |   |   |   |   |   |   |   |
b α1C: ...Val Thr Ser Ala Lys Asn Lys Thr His Phe Ser Val Arg Leu Leu Lys

h α1C: ...Phe Ser Arg Glu Lys Lys Ala Ala Lys Thr Leu Gly Ile Val Val Gly
           |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
b α1C: ...Phe Ser Arg Glu Lys Lys Ala Ala Lys Thr Leu Gly Ile Val Val Gly

h α1C: ...Cys Phe Val Leu............
           |   |   |   |
b α1C: ...Cys Phe Val Leu Cys Trp Leu Pro Phe Leu Val Met Pro
```

FIG.2

1 GAATTCCCTC CTAGAAGCTG GAGAGAGCAG GAGCCTTCGG TGGGGCAGCT CAAAATGTAG 60

61 GTAACTGCGG GCCAGGAGCA GCGCCCAGAT GCCATCGGTC CCTGCCTTTG AGCGTCGACG 120

121 GCTGATCTTT TGGTTTGAGG GAGAGACTGG CGCTGGAGTT TTGAATTCCG AATCATGTGC 180

181 AGAATCGTGA ATCTTCCCCC AGCCAGGACG AATAAGACAG CGCGGAAAAG CAGATTCTCG 240

241 TAATTCTGGA ATTGCATGTT GCAAGGAGTC TCCTGGATCT TCGCACCCAG CTTCGGGTAC 300

301 GGGAGGGAGT CCGGGTCCCG GCTAGGCCAG CCCGCAGGTG GAGAGGGTCC CCGGCAGCCC 360

361 CGCGCGCCCC TGGCCATGTC TTTAATGCCC TGCCCCTTCA TGTGGCCTTC TGAGGGTTCC 420

421 CAGGGCTGGC CAGGGTTGTC TCCCACCCGC GCGCGCCGTC TCACCCCCAG CCAAACCCAC 480

481 CTGGCAGGGC TCCCTCCAGA AGAGACCTTT TGATTCCCGG CTCCCGCGCT CCCGCCTCCG 540

541 CGCCAGCCCG GGAGGTGGCC CTGGACAGCC GGACCTCGCC CGGCCCCGGC TGNGGACCAT 600

601 GGTGTTTCTC TCGGGAAATG CTTCCGACAG CTCCAACTGC ACCCAACCGC CGGCACCGGT 660

661 GAACATTTCC AAGGCCATTC TGCTCGGGGT GATCTTGGGG GGCCTCATTC TTTTCGGGGT 720

721 GCTGGGTAAC ATCCTAGTGA TCCTCTCCGT AGCCTGTCAC CGACACCTGC ACTCAGTCAC 780

781 GCACTACTAC ATCGTCAACC TGGCGGTGGC CGACCTCCTG CTCACCTCCA CGGTGCTGCC 840

841 CTTCTCCGCC ATCTTCGAGG TCCTAGGCTA CTGGGCCTTC GGCAGGGTCT TCTGCAACAT 900

901 CTGGGCGGCA GTGGATGTGC TGTGCTGCAC CGCGTCCATC ATGGGCCTCT GCATCATCTC 960

961 CATCGACCGC TACATCGGCG TGAGCTACCC GCTGCGCTAC CCAACCATCG TCACCCAGAG 1020

1021 GAGGGGTCTC ATGGCTCTGC TCTGCGTCTG GGCACTCTCC CTGGTCATAT CCATTGGACC 1080

1081 CCTCTTCGGC TGGAGGCAGC CGGCCCCCGA GGACGAGACC ATCTGCCAGA TCAACGAGGA 1140

1141 GCCGGGCTAC GTGCTCTTCT CGGCTCTGGG CTCCTTCTAC CTGCCTCTGG CCATCATCCT 1200

FIG.3A

1201 GGTCATGTAC TGCCGCGTCT ACGTGGTGGC CAAGAGGGAG AGCCGGGGCC TCAAGTCTGG 1260

1261 CCTCAAGACC GACAAGTCGG ACTCGGAGCA AGTGACGCTC CGCATCCATC GGAAAAACGC 1320

1321 CCCGGCAGGA GGCAGCGGGA TGGCCAGCGC CAAGACCAAG ACGCACTTCT CAGTGAGGCT 1380

1381 CCTCAAGTTC TCCCGGGAGA AGAAAGCGGC CAAAACGCTG GGCATCGTGG TCGGCTGCTT 1440

1441 CGTCCTCTGC TGGCTGCCTT TTTTCTTAGT CATGCCCATT GGGTCTTTCT TCCCTGATTT 1500

1501 CAAGCCCTCT GAAACAGTTT TTAAAATAGT ATTTTGGCTC GGATATCTAA ACAGCTGCAT 1560

1561 CAACCCCATC ATATACCCAT GCTCCAGCCA AGAGGGAATTCC

FIG.3B

1 CTGATTTCAA GCCCTCTGAA ACAGTTTTTA AAATAGTATT TTGGCTCGGA TATCTAAACA 60

61 GCTGCATCAA CCCCATCATA TACCCATGCT CCAGCCAAGA GTTCAAAAAG GCCTTTCAGA 120

121 ATGTCTTGAG AATCCAGTGT CTCCGCAGAA AGCAGTCTTC CAAACATGCC CTGGGCTACA 180

181 CCCTGCACCC GCCCAGCCAG GCCGTGGAAG GGCAACACAA GGACATGGTG CGCATCCCCG 240

241 TGGGATCAAG AGAGACCTTC TACAGGATCT CCAAGACGGA TGGCGTTTGT GAATGGAAAT 300

301 TTTTCTCTTC CATGCCCCGT GGATCTGCCA GGATTACAGT GTCCAAAGAC CAATCCTCCT 360

361 GTACCACAGC CCGGGTGAGA AGTAAAAGCT TTTTGCAGGT CTGCTGCTGT GTAGGGCCCT 420

421 CAACCCCCAG CCTTGACAAG AACCATCAAG TTCCAACCAT TAAGGTCCAC ACCATCTCCC 480

481 TCAGTGAgAA CGGcGAaGAg GTtTAAGAAT TC 512

FIG.4

1 GAATTCCCTC CTAGAAGCTG GAGAGAGCAG GAGCCTTCGG TGGGGCAGCT

51 CAAAATGTAG GTAACTGCGG GCCAGGAGCA GCGCCCAGAT GCCATCGGTC

101 CCTGCCTTTG AGCGTCGACG GCTGATCTTT TGGTTTGAGG GAGAGACTGG

151 CGCTGGAGTT TTGAATTCCG AATCATGTGC AGAATCGTGA ATCTTCCCCC

201 AGCCAGGACG AATAAGACAG CGCGGAAAAG CAGATTCTCG TAATTCTGGA

251 ATTGCATGTT GCAAGGAGTC TCCTGGATCT TCGCACCcAG CTTCGGGTAC

301 GGGAGGGAGT CCGGGTCCCG GCTAGGCCAG CCCGCAGGTG GAGAGGGTCC

351 CCGGCAGCCC CGCGCGCCCC TGGCCATGTC TTTAATGCCC TGCCCCTTCA

401 TGTGGCCTTC TGAGGGTTCC CAGGGCTGGC CAGGGTTGTC TCCCACCCGC

451 GCGCGCCGTC TCACCCCCAG CCAAACCCAC CTGGCAGGGC TCCCTCCAGA

501 AGAGACCTTT TGATTCCCGG CTCCCGCGCT CCCGCCTCCG CGCCAGCCCG

551 GGAGGTGGCC CTGGACAGCC GGACCTCGCC CGGCCCCGGC TGNGGACCAT

601 GGTGTTTCTC TCGGGAAATG CTTCCGACAG CTCCAACTGC ACCCAACCGC

651 CGGCACCGGT GAACATTTCC AAGGCCATTC TGCTCGGGGT GATCTTGGGG

701 GGCCTCATTC TTTTCGGGGT GCTGGGTAAC ATCCTAGTGA TCCTCTCCGT

751 AGCCTGTCAC CGACACCTGC ACTCAGTCAC GCACTACTAC ATCGTCAACC

801 TGGCGGTGGC CGACCTCCTG CTCACCTCCA CGGTGCTGCC CTTCTCCGCC

851 ATCTTCGAGG TCCTAGGCTA CTGGGCCTTC GGCAGGGTCT TCTGCAACAT

901 CTGGGCGGCA GTGGATGTGC TGTGCTGCAC CGCGTCCATC ATGGGCCTCT

951 GCATCATCTC CATCGACCGC TACATCGGCG TGAGCTACCC GCTGCGCTAC

FIG.5A

1001 CCAACCATCG TCACCCAGAG GAGGGGTCTC ATGGCTCTGC TCTGCGTCTG

1051 GGCACTCTCC CTGGTCATAT CCATTGGACC CCTCTTCGGC TGGAGGCAGC

1101 CGGCCCCCGA GGACGAGACC ATCTGCCAGA TCAACGAGGA GCCGGGCTAC

1151 GTGCTCTTCT CGGCTCTGGG CTCCTTCTAC CTGCCTCTGG CCATCATCCT

1201 GGTCATGTAC TGCCGCGTCT ACGTGGTGGC CAAGAGGGAG AGCCGGGGCC

1251 TCAAGTCTGG CCTCAAGACC GACAAGTCGG ACTCGGAGCA AGTGACGCTC

1301 CGCATCCATC GGAAAAACGC CCCGGCAGGA GGCAGCGGGA TGGCCAGCGC

1351 CAAGACCAAG ACGCACTTCT CAGTGAGGCT CCTCAAGTTC TCCCGGGAGA

1401 AGAAAGCGGC CAAAACGCTG GGCATCGTGG TCGGCTGCTT CGTCCTCTGC

1451 TGGCTGCCTT TTTTCTTAGT CATGCCCATT GGGTCTTTCT TCCCTGATTT

1501 CAAGCCCTCT GAAACAGTTT TTAAAATAGT ATTTTGGCTC GGATATCTAA

1551 ACAGCTGCAT CAACCCCATC ATATACCCAT GCTCCAGCCA AGAGTTCAAA

1601 AAGGCCTTTC AGAATGTCTT GAGAATCCAG TGTCTCCGCA GAAAGCAGTC

1651 TTCCAAACAT GCCCTGGGCT ACACCCTGCA CCCGCCCAGC CAGGCCGTGG

1701 AAGGGCAACA CAAGGACATG GTGCGCATCC CCGTGGGATC AAGAGAGACC

1751 TTCTACAGGA TCTCCAAGAC GGATGGCGTT TGTGAATGGA AATTTTTCTC

1801 TTCCATGCCC CGTGGATCTG CCAGGATTAC AGTGTCCAAA GACCAATCCT

1851 CCTGTACCAC AGCCCGGGTG AGAAGTAAAA GCTTTTTGCA GGTCTGCTGC

1901 TGTGTAGGGC CCTCAACCCC CAGCCTTGAC AAGAACCATC AAGTTCCAAC

1951 CATTAAGGTC CACACCATCT CCCTCAGTGA GAACGGCGAA GAGGTTTAAG

2001 AATTC

FIG.5B

1 MetValPheLeuSerGlyAsnAlaSerAsp SerSerAsnCysThrGlnProProAlaPro 20

21 ValAsnIleSerLysAlaIleLeuLeuGly ValIleLeuGlyGlyLeuIleLeuPheGly 40

41 ValLeuGlyAsnIleLeuValIleLeuSer ValAlaCysHisArgHisLeuHisSerVal 60

61 ThrHisTyrTyrIleValAsnLeuAlaVal AlaAspLeuLeuLeuThrSerThrValLeu 80

81 ProPheSerAlaIlePheGluValLeuGly TyrTrpAlaPheGlyArgValPheCysAsn 100

101 IleTrpAlaAlaValAspValLeuCysCys ThrAlaSerIleMetGlyLeuCysIleIle 120

121 SerIleAspArgTyrIleGlyValSerTyr ProLeuArgTyrProThrIleValThrGln 140

141 ArgArgGlyLeuMetAlaLeuLeuCysVal TrpAlaLeuSerLeuValIleSerIleGly 160

161 ProLeuPheGlyTrpArgGlnProAlaPro GluAspGluThrIleCysGlnIleAsnGlu 180

181 GluProGlyTyrValLeuPheSerAlaLeu GlySerPheTyrLeuProLeuAlaIleIle 200

201 LeuValMetTyrCysArgValTyrValVal AlaLysArgGluSerArgGlyLeuLysSer 220

221 GlyLeuLysThrAspLysSerAspSerGlu GlnValThrLeuArgIleHisArgLysAsn 240

241 AlaProAlaGlyGlySerGlyMetAlaSer AlaLysThrLysThrHisPheSerValArg 260

261 LeuLeuLysPheSerArgGluLysLysAla AlaLysThrLeuGlyIleValValGlyCys 280

281 PheValLeuCysTrpLeuProPhePheLeu ValMetProIleGlySerPhePheProAsp 300

301 PheLysProSerGluThrValPheLysIle ValPheTrpLeuGlyTyrLeuAsnSerCys 320

321 IleAsnProIleIleTyrProCysSerSer GlnGluPheLysLysAlaPheGlnAsnVal 340

341 LeuArgIleGlnCysLeuArgArgLysGln SerSerLysHisAlaLeuGlyTyrThrLeu 360

361 HisProProSerGlnAlaValGluGlyGln HisLysAspMetValArgIleProValGly 380

FIG.6A

381 SerArgGluThrPheTyrArgIleSerLys ThrAspGlyValCysGluTrpLysPhePhe 400

401 SerSerMetProArgGlySerAlaArgIle ThrValSerLysAspGlnSerSerCysThr 420

421 ThrAlaArgValArgSerLysSerPheLeu GlnValCysCysCysValGlyProSerThr 440

441 ProSerLeuAspLysAsnHisGlnValPro ThrIleLysValHisThrIleSerLeuSer 460

461 GluAsnGlyGluGluValEnd 467

FIG.6B

```
1    AAT TCC CTC CTA GAA GCT GGA GAG AGC AGG AGC CTT CGG TGG GCC   45

46   AGC TCA AAA TGT AGG TAA CTG CGG GCC AGG AGC AGC GCC CAG ATG   90

91   CCA TCG GTC CCT GCC TTT GAG CGT CGA CGG CTG ATC TTT TGG TTT  135

136  GAG GGA GAG ACT GGC GCT GGA GTT TTG AAT TCC GAA TCA TGT GCA  180

181  GAA TCG TGA ATC TTC CCC CAG CCA GGA CGA ATA AGA CAG CGC GGA  225

226  AAA GCA GAT TCT CGT AAT TCT GGA ATT GCA TGT TGC AAG GAG TCT  270

271  CCT GGA TCT TCG CAC CCA GCT TCG GGT ACG GGA GGG AGT CCG GGT  315

316  CCC GGC TAG GCC AGC CCG CAG GTG GAG AGG GTC CCC GGC AGC CCC  360

361  GCG CGC CCC TGG CCA TGT CTT TAA TGC CCT GCC CCT TCA TGT GGC  405

406  CTT CTG AGG GTT CCC AGG GCT GGC CAG GGT TGT CTC CCA CCC GCG  450

451  CGC GCC GTC TCA CCC CCA GCC AAA CCC ACC TGG CAG GGC TCC CTC  495

496  CAG AAG AGA CCT TTT GAT TCC CGG CTC CCG CGC TCC CGC CTC CGC  540

541  GCC AGC CCG GGA GGT GGC CCT GGA CAG CCG GAC CTC GCC CGG CCC  585

586  CGG CTG NGG ACC ATG GTG TTT CTC TCG GGA AAT GCT TCC GAC AGC  630
1                    Met Val Phe Leu Ser Gly Asn Ala Ser Asp Ser   11

631  TCC AAC TGC ACC CAA CCG CCG GCA CCG GTG AAC ATT TCC AAG GCC  675
12   Ser Asn Cys Thr Gln Pro Pro Ala Pro Val Asn Ile Ser Lys Ala   26

676  ATT CTG CTC GGG GTG ATC TTG GGG GGC CTC ATT CTT TTC GGG GTG  720
27   Ile Leu Leu Gly Val Ile Leu Gly Gly Leu Ile Leu Phe Gly Val   41

721  CTG GGT AAC ATC CTA GTG ATC CTC TCC GTA GCC TGT CAC CGA CAC  765
42   Leu Gly Asn Ile Leu Val Ile Leu Ser Val Ala Cys His Arg His   56

766  CTG CAC TCA GTC ACG CAC TAC TAC ATC GTC AAC CTG GCG GTG GCC  810
57   Leu His Ser Val Thr His Tyr Tyr Ile Val Asn Leu Ala Val Ala   71
```

FIG.7A

811 GAC CTC CTG CTC ACC TCC ACG GTG CTG CCC TTC TCC GCC ATC TTC 855
72 Asp Leu Leu Leu Thr Ser Thr Val Leu Pro Phe Ser Ala Ile Phe 86

856 GAG GTC CTA GGC TAC TGG GCC TTC GGC AGG GTC TTC TGC AAC ATC 900
87 Glu Val Leu Gly Tyr Trp Ala Phe Gly Arg Val Phe Cys Asn Ile 101

901 TGG GCG GCA GTG GAT GTG CTG TGC TGC ACC GCG TCC ATC ATG GGC 945
102 Trp Ala Ala Val Asp Val Leu Cys Cys Thr Ala Ser Ile Met Gly 116

946 CTC TGC ATC ATC TCC ATC GAC CGC TAC ATC GGC GTG AGC TAC CCG 990
117 Leu Cys Ile Ile Ser Ile Asp Arg Tyr Ile Gly Val Ser Tyr Pro 131

991 CTG CGC TAC CCA ACC ATC GTC ACC CAG AGG AGG GGT CTC ATG GCT 1035
132 Leu Arg Tyr Pro Thr Ile Val Thr Gln Arg Arg Gly Leu Met Ala 146

1036 CTG CTC TGC GTC TGG GCA CTC TCC CTG GTC ATA TCC ATT GGA CCC 1080
147 Leu Leu Cys Val Trp Ala Leu Ser Leu Val Ile Ser Ile Gly Pro 161

1081 CTC TTC GGC TGG AGG CAG CCG GCC CCC GAG GAC GAG ACC ATC TGC 1125
162 Leu Phe Gly Trp Arg Gln Pro Ala Pro Glu Asp Glu Thr Ile Cys 176

1126 CAG ATC AAC GAG GAG CCG GGC TAC GTG CTC TTC TCG GCT CTG GGC 1170
177 Gln Ile Asn Glu Glu Pro Gly Tyr Val Leu Phe Ser Ala Leu Gly 191

1171 TCC TTC TAC CTG CCT CTG GCC ATC ATC CTG GTC ATG TAC TGC CGC 1215
192 Ser Phe Tyr Leu Pro Leu Ala Ile Ile Leu Val Met Tyr Cys Arg 206

1216 GTC TAC GTG GTG GCC AAG AGG GAG AGC CGG GGC CTC AAG TCT GGC 1260
207 Val Tyr Val Val Ala Lys Arg Glu Ser Arg Gly Leu Lys Ser Gly 221

1261 CTC AAG ACC GAC AAG TCG GAC TCG GAG CAA GTG ACG CTC CGC ATC 1305
222 Leu Lys Thr Asp Lys Ser Asp Ser Glu Gln Val Thr Leu Arg Ile 236

1306 CAT CGG AAA AAC GCC CCG GCA GGA GGC AGC GGG ATG GCC AGC GCC 1350
237 His Arg Lys Asn Ala Pro Ala Gly Gly Ser Gly Met Ala Ser Ala 251

1351 AAG ACC AAG ACG CAC TTC TCA GTG AGG CTC CTC AAG TTC TCC CGG 1395
252 Lys Thr Lys Thr His Phe Ser Val Arg Leu Leu Lys Phe Ser Arg 266

1396 GAG AAG AAA GCG GCC AAA ACG CTG GGC ATC GTG GTC GGC TGC TTC 1440
267 Glu Lys Lys Ala Ala Lys Thr Leu Gly Ile Val Val Gly Cys Phe 281

FIG.7B

1441 GTC CTC TGC TGG CTG CCT TTT TTC TTA GTC ATG CCC ATT GGG TCT 1485
282 Val Leu Cys Trp Leu Pro Phe Phe Leu Val Met Pro Ile Gly Ser 296

1486 TTC TTC CCT GAT TTC AAG CCC TCT GAA ACA GTT TTT AAA ATA GTA 1530
297 Phe Phe Pro Asp Phe Lys Pro Ser Glu Thr Val Phe Lys Ile Val 311

1531 TTT TGG CTC GGA TAT CTA AAC AGC TGC ATC AAC CCC ATC ATA TAC 1575
312 Phe Trp Leu Gly Tyr Leu Asn Ser Cys Ile Asn Pro Ile Ile Tyr 326

1576 CCA TGC TCC AGC CAA GAG TTC AAA AAG GCC TTT CAG AAT GTC TTG 1620
327 Pro Cys Ser Ser Gln Glu Phe Lys Lys Ala Phe Gln Asn Val Leu 341

1621 AGA ATC CAG TGT CTC CGC AGA AAG CAG TCT TCC AAA CAT GCC CTG 1665
342 Arg Ile Gln Cys Leu Arg Arg Lys Gln Ser Ser Lys His Ala Leu 356

1666 GGC TAC ACC CTG CAC CCG CCC AGC CAG GCC GTG GAA GGG CAA CAC 1710
357 Gly Tyr Thr Leu His Pro Pro Ser Gln Ala Val Glu Gly Gln His 371

1711 AAG GAC ATG GTG CGC ATC CCC GTG GGA TCA AGA GAG ACC TTC TAC 1755
372 Lys Asp Met Val Arg Ile Pro Val Gly Ser Arg Glu Thr Phe Tyr 386

1756 AGG ATC TCC AAG ACG GAT GGC GTT TGT GAA TGG AAA TTT TTC TCT 1800
387 Arg Ile Ser Lys Thr Asp Gly Val Cys Glu Trp Lys Phe Phe Ser 401

1801 TCC ATG CCC CGT GGA TCT GCC AGG ATT ACA GTG TCC AAA GAC CAA 1845
402 Ser Met Pro Arg Gly Ser Ala Arg Ile Thr Val Ser Lys Asp Gln 416

1846 TCC TCC TGT ACC ACA GCC CGG GTG AGA AGT AAA AGC TTT TTG CAG 1890
417 Ser Ser Cys Thr Thr Ala Arg Val Arg Ser Lys Ser Phe Leu Gln 431

1891 GTC TGC TGC TGT GTA GGG CCC TCA ACC CCC AGC CTT GAC AAG AAC 1935
432 Val Cys Cys Cys Val Gly Pro Ser Thr Pro Ser Leu Asp Lys Asn 446

1936 CAT CAA GTT CCA ACC ATT AAG GTC CAC ACC ATC TCC CTC AGT GAG 1980
447 His Gln Val Pro Thr Ile Lys Val His Thr Ile Ser Leu Ser Glu 461

1981 AAC GGC GAA GAG GTT TAA GAA TTC 2004
462 Asn Gly Glu Glu Val End 668

FIG.7C

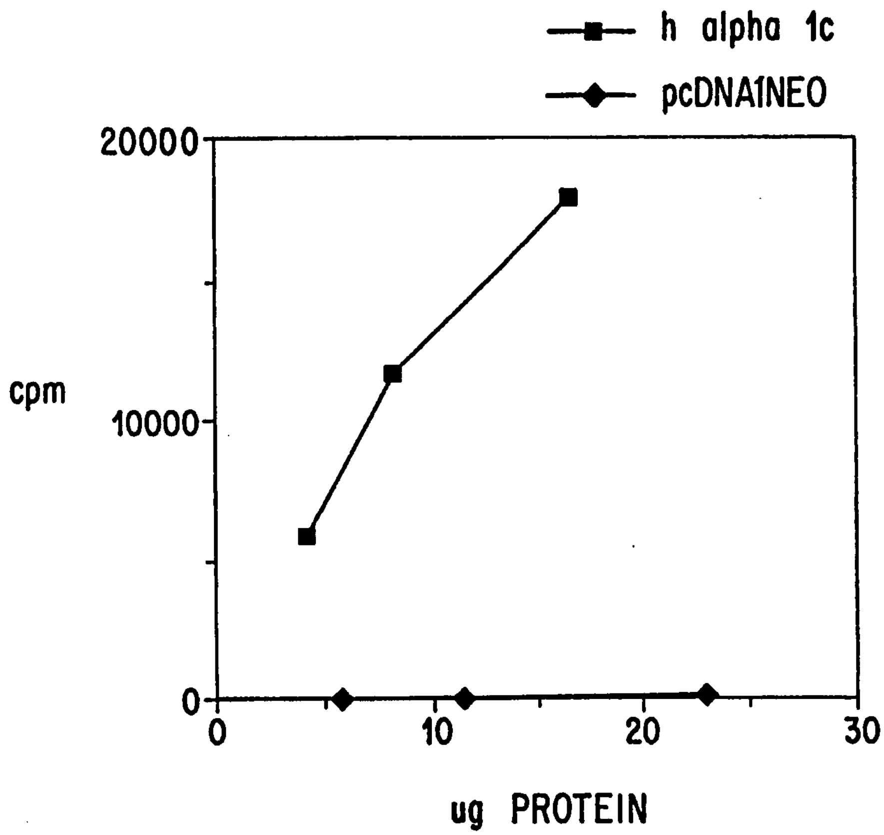


FIG. 8

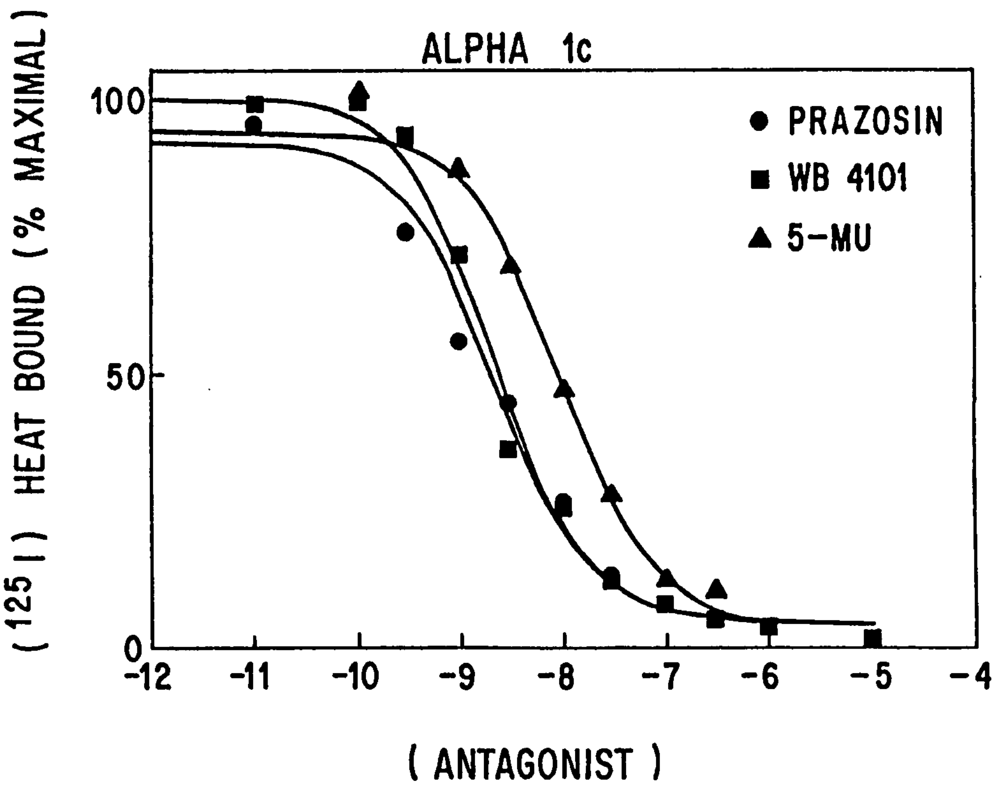

ALPHA 1c
(125 I) HEAT BOUND (% MAXIMAL)
100
50
0
-12
-11
-10
-9
-8
-7
-6
-5
-4
(ANTAGONIST)
PRAZOSIN
WB 4101
5-MU

FIG. 9

1 CCCGTGCAGG GGCCCTACGG ACACCACCAG GGCTACGACC CAGAGCAGGG CCAGGATGGC 60

61 GGCCGCCTTG CGCTCGGTCA TGATGGCTGG GTACTTGAGT GAGTGGCGCA CGCCCACGTA 120

121 CCGGTCCACG GAGATGGTGC AGAGGCTGAG GATGGAGGCC GTGCAGCACA GCACGTCCAC 180

181 GGCGGCCGTC GGGGGACTGG TGGTGAGCGC GCAGGGCGTG GGCGTGGGCG TCTTCCTGGC 240

241 AGCCTTCATC CTTATGGCCG TGGCAGGTAA CCTGCTTGTC ATCCTCTCAG TGGCCTGCAA 300

301 CCGCCACCTG CAGACCGTCA CCAACTATTT CATCGTGAAC CTGGCCGTGG CCGACCTGCT 360

361 GCTGAGCGCC ACCGTACTGC CCTTCTCGGC CACCATGGAG GTTCTGGGCT TCTGGGCCTT 420

421 TGGCCGCGCC TTCTGCGACG TATGGGCCGC CGTGGACGTG CTGTGCTGCA CGGCCTCCAT 480

481 CCTCAGCCTC TGCACCATCT CCGTGGACCG GTACGTGGGC GTGCGCCACT CACTCAAGTA 540

541 CCCAGCCATC ATGACCGAGC GCAAGGCGGC CGCCATCCTG GCCCTGCTCT GGGTCGTAGC 600

601 CCTGGTGGTG TCCGTAGGGC CCCTGCTGGG CTGGAAGGAG CCCGTGCCCC CTGACGAGCG 660

661 CTTCTGCGGT ATCACCGAGG AGGCGGGCTA CGCTGTCTTC TCCTCCGTGT GCTCCTTCTA 720

721 CCTGCCCATG GCGGTCATCG TGGTCATGTA CTGCCGCGTG TACGTGGTCG CGCGCAGCAC 780

781 CACGCGCAGC CTCGAGGCAG GCGTCAAGCG CGAGCGAGGC AAGGCCTCCG AGGTGGTGCT 840

FIG.10A

841 GCGCATCCAC TGTCGCGGCG CGGCCACGGG CGCCGACGGG GCGCACGGCA TGCGCAGCGC 900

901 CAAGGGCCAC ACCTTCCGCA GCTCGCTCTC CGTGCGCCTG CTCAAGTTCT CCCGTGAGAA 960

961 GAAAGCGGCC AAGACTCTGG CCATCGTCGT GGGTGTCTTC GTGCTCTGCT GGTTCCCTTT 1020

1021 CTTCTTTGTC CTGCCGCTCG GCTCCTTGTT CCCGCAGCTG AAGCCATCGG AGGGCGTCTT 1080

1081 CAAGGTCATC TTCTGGCTCG GCTACTTCAA CAGCTGCGTG AACCCGCTCA TCTACCCCTG 1140

1141 TTCCAGCCGC GAGTTCAAGC GCGCCTTCCT CCGTCTCCTG CGCTGCCAGT GCCGTCGTCG 1200

1201 CCGGCGCCGC CGCCCTCTCT GGCGTGTCTA CGGCCACCAC TGGCGGGCCT CCACCAGCGG 1260

1261 CCTGCGCCAG GACTGCGCCC CGAGTTCGGG CGACGCGCCC CCCGGAGCGC CGCTGGCCCT 1320

1321 CACCGCGCTC CCCGACCCCG ACCCCGAACC CCCAGGCACG CCCGAGATGC AGGCTCCGGT 1380

1381 CGCCAGCCGT CGAAGCCACC CAGCGCCTTC CGCGAGTGGA GGCTGCTGGG GCCGTTCCGG 1440

1441 AGACCCACGA CCCAGCTGCG CGCCAAAGTC GCCAGCCTGT CGCACAAGAT CGCCGCCGGG 1500

1501 GGCGCGCAGC GCGCAGAGGC AGCGTGCGCC CAGCGCTCAG AGGTGGAGGC TGTGTCCCTA 1560

1561 GGCGTCCCAC ACGAGGTGGC CGAGGGCGCC ACCTGCCAGG CCTACGAATT GGCCGACTAC 1620

1621 A 1621

FIG.10B

1 MetAlaAlaAlaLeuArgSerValMetMet AlaGlyTyrLeuSerGluTrpArgThrPro 20

21 ThrTyrArgSerThrGluMetValGlnArg LeuArgMetGluAlaValGlnHisSerThr 40

41 SerThrAlaAlaValGlyGlyLeuValVal SerAlaGlnGlyValGlyValGlyValPhe 60

61 LeuAlaAlaPheIleLeuMetAlaValAla GlyAsnLeuLeuValIleLeuSerValAla 80

81 CysAsnArgHisLeuGlnThrValThrAsn TyrPheIleValAsnLeuAlaValAlaAsp 100

101 LeuLeuLeuSerAlaThrValLeuProPhe SerAlaThrMetGluValLeuGlyPheTrp 120

121 AlaPheGlyArgAlaPheCysAspValTrp AlaAlaValAspValLeuCysCysThrAla 140

141 SerIleLeuSerLeuCysThrIleSerVal AspArgTyrValGlyValArgHisSerLeu 160

161 LysTyrProAlaIleMetThrGluArgLys AlaAlaAlaIleLeuAlaLeuLeuTrpVal 180

181 ValAlaLeuValValSerValGlyProLeu LeuGlyTrpLysGluProValProProAsp 200

201 GluArgPheCysGlyIleThrGluGluAla GlyTyrAlaValPheSerSerValCysSer 220

221 PheTyrLeuProMetAlaValIleValVal MetTyrCysArgValTyrValValAlaArg 240

241 SerThrThrArgSerLeuGluAlaGlyVal LysArgGluArgGlyLysAlaSerGluVal 260

261 ValLeuArgIleHisCysArgGlyAlaAla ThrGlyAlaAspGlyAlaHisGlyMetArg 280

281 SerAlaLysGlyHisThrPheArgSerSer LeuSerValArgLeuLeuLysPheSerArg 300

301 GluLysLysAlaAlaLysThrLeuAlaIle ValValGlyValPheValLeuCysTrpPhe 320

321 ProPhePhePheValLeuProLeuGlySer LeuPheProGlnLeuLysProSerGluGly 340

341 ValPheLysValIlePheTrpLeuGlyTyr PheAsnSerCysValAsnProLeuIleTyr 360

361 ProCysSerSerArgGluPheLysArgAla PheLeuArgLeuLeuArgCysGlnCysArg 380

381 ArgArgArgArgArgArgProLeuTrpArg ValTyrGlyHisHisTrpArgAlaSerThr 400

FIG.11A

401 SerGlyLeuArgGlnAspCysAlaProSer SerGlyAspAlaProProGlyAlaProLeu 420

421 AlaLeuThrAlaLeuProAspProAspPro GluProProGlyThrProGluMetGlnAla 440

441 ProValAlaSerArgArgSerHisProAla ProSerAlaSerGlyGlyCysTrpGlyArg 460

461 SerGlyAspProArgProSerCysAlaPro LysSerProAlaCysArgThrArgSerPro 480

481 ProGlyAlaArgSerAlaGlnArgGlnArg AlaProSerAlaGlnArgTrpArgLeuCys 500

501 Pro

FIG.11B

TCTAGACCATGAATCCCGACCTGGACACCGGCCACAACACATCAGCACCTGCCCACTGGGGAGAGTTG

AAAAATGCCAACTTCACTGGCCCCAACCAGACCTCGAGCAACTCCACACTGCCCCAGCTG

GACATCACCAGGGCCATCTCTGTGGGCCTGGTGCTGGGCGCCTTCATCCTCTTTGCCATC

GTGGGCAACATCCTAGTCATCTTGTCTGTGGCCTGCAACCGGCACCTGCGGACGCCCACC

AACTACTTCATTGTCAACCTGGCCATGGCCGACCTGCTGTTGAGCTTCACCGTCCTGCCC

TTCTCAGCGGCCCTAGAGGTGCTCGGCTACTGGGTGCTGGGGCGGATCTTCTGTGACATC

TGGGCAGCCGTGGATGTCCTGTGCTGCACAGCGTCCATTCTGAGCCTGTGCGCCATCTCC

ATCGATCGCTACATCGGGGTGCGCTACTCTCTGCAGTATCCCACGCTGGTCACCCGGAGG

AAGGCCATCTTGGCCCTGCTCAGTGTCTGGGTCTTGTCCACCGTCATCTCCATCGGGCCT

CTCCTTGGGTGGAAGGAGCCGGCACCCAACGATGACAAGGAGTGCGGGGTCACCGAAGAA

CCCTTCTATGCCCTCTTCTCCTCTCTGGGCTCCTTCTACATCCCTCTGGCGGTCATTCTA

GTCATGTACTGCCGTGTCTATATAGTGGCCAAGAGAACCACCAAGAACCTAGAGGCAGGA

GTCATGAAGGAGATGTCCAACTCCAAGGAGCTGACCCTGAGGATCCATTCCAAGAACTTT

CACGAGGACACCCTTAGCAGTACCAAGGCCAAGGGCCACAACCCCAGGAGTTCCATAGCT

GTCAAACTTTTTAAGTTCTCCAGGGAAAAGAAAGCAGCTAAGACGTTGGGCATTGTGGTC

GGTATGTGAATTC

FIG.12

1 AAGAGAACCA CCAAGAACCT AGAGGCAGGA GTCATGAAGG AGATGTCCAA CTCCAAGGAG 60

61 CTGACCCTGA GGATCCATTC CAAGAACTTT CACGAGGACA CCCTTAGCAG TACCAAGGCC 120

121 AAGGGCCACA ACCCCAGGAG TTCCATAGCT GTCAAACTTT TTAAGTTCTC CAGGGAAAAG 180

181 AAAGCAGCTA AGACGTTGGG CATTGTGGTC GGTATGTTCA TCTTGTGCTG GCTACCCTTC 240

241 TTCATCGCTC TACCGCTTGG CTCCTTGTTC TCCACCCTGA AGCCCCCCGA CGCCGTGTTC 300

301 AAGGTGGTGT TCTGGCTGGG CTACTTCAAC AGCTGCCTCA ACCCCATCAT CTACCCATGC 360

361 TCCAGCAAGG AGTTCAAGCG CGCTTTCGT 389

FIG.13

GAATTCATGA TTCAAGGTGG TGTTCTGGCT GGGCTACTTC AACAGCTGCC TCAATCCCAT CATCTACCCG

TGCTCCAGCA AGGAGTTCAA GCGCGCCTTC ATGCGTATCC TTGGGTGCCA GTGCCGCGGT GGCCGCCGCC

GCCGCCGCCG TCGCCGTCTA GGCGCGTGCG CTTACACCTA CCGGCCGTGG ACCCGCGGCG GCTCGCTGGA

GAGATCACAG TCGCGGAAGG ACTCTCTGGA TGACAGCGGC AGCTGCATGA GCGGCCAGAA GAGGACCCTG

CCCTCGGCGT CGCCCAGCCC GGGCTACCTG GGTCGAGGAA CGCAGCCACC CGTGGAGCTG TGCGCCTTCC

CCGAGTGGAA ACCCGGGGCG CTGCTCAGCT TGCCAGAGCC TCCTGGCCGC CGCGGCCGTC TCGACTCTGG

GCCACTCTTC ACCTTCAAGC TCCTGGGCGA TCCTGAGAGC CCGGGAACCG AAGCGACAGC CAGCAACGGG

GGCTGCGACA CCACGACCGA CCTGGCCAAC GGGCAGCCCG GCTTCAAGAG CAACATGCCC CTGGGCCCGG

GCCACTTTTA AAAGCCGAATTC

FIG.14

1 TCTAGACCAT GAATCCCGAC CTGGACACCG GCCACAACAC ATCAGCACCT

51 GCCCACTGGG GAGAGTTGAA AAATGCCAAC TTCACTGGCC CCAACCAGAC

101 CTCGAGCAAC TCCACACTGC CCCAGCTGGA CATCACCAGG GCCATCTCTG

151 TGGGCCTGGT GCTGGGCGCC TTCATCCTCT TTGCCATCGT GGGCAACATC

201 CTAGTCATCT TGTCTGTGGC CTGCAACCGG CACCTGCGGA CGCCCACCAA

251 CTACTTCATT GTCAACCTGG CCATGGCCGA CCTGCTGTTG AGCTTCACCG

301 TCCTGCCCTT CTCAGCGGCC CTAGAGGTGC TCGGCTACTG GGTGCTGGGG

351 CGGATCTTCT GTGACATCTG GGCAGCCGTG GATGTCCTGT GCTGCACAGC

401 GTCCATTCTG AGCCTGTGCG CCATCTCCAT CGATCGCTAC ATCGGGGTGC

451 GCTACTCTCT GCAGTATCCC ACGCTGGTCA CCCGGAGGAA GGCCATCTTG

501 GCCCTGCTCA GTGTCTGGGT CTTGTCCACC GTCATCTCCA TCGGGCCTCT

551 CCTTGGGTGG AAGGAGCCGG CACCCAACGA TGACAAGGAG TGCGGGGTCA

601 CCGAAGAACC CTTCTATGCC CTCTTCTCCT CTCTGGGCTC CTTCTACATC

651 CCTCTGGCGG TCATTCTAGT CATGTACTGC CGTGTCTATA TAGTGGCCAA

701 GAGAACCACC AAGAACCTAG AGGCAGGAGT CATGAAGGAG ATGTCCAACT

751 CCAAGGAGCT GACCCTGAGG ATCCATTCCA AGAACTTTCA CGAGGACACC

801 CTTAGCAGTA CCAAGGCCAA GGGCCACAAC CCCAGGAGTT CCATAGCTGT

851 CAAACTTTTT AAGTTCTCCA GGGAAAAGAA AGCAGCTAAG ACGTTGGGCA

901 TTGTGGTCGG TATGTTCATC TTGTGCTGGC TACCCTTCTT CATCGCTCTA

951 CCGCTTGGCT CCTTGTTCTC CACCCTGAAG CCCCCCGACG CCGTGTTCAA

FIG.15A

1001 GGTGGTGTTC TGGCTGGGCT ACTTCAACAG CTGCCTCAAC CCCATCATCT

1051 ACCCATGCTC CAGCAAGGAG TTCAAGCGCG CCTTCATGCG TATCCTTGGG

1101 TGCCAGTGCC GCGGTGGCCG CCGCCGCCGC CGCCGTCGCC GTCTAGGCGC

1151 GTGCGCTTAC ACCTACCGGC CGTGGACCCG CGGCGGCTCG CTGGAGAGAT

1201 CACAGTCGCG GAAGGACTCT CTGGATGACA GCGGCAGCTG CATGAGCGGC

1251 CAGAAGAGGA CCCTGCCCTC GGCGTCGCCC AGCCCGGGCT ACCTGGGTCG

1301 AGGAACGCAG CCACCCGTGG AGCTGTGCGC CTTCCCCGAG TGGAAACCCG

1351 GGGCGCTGCT CAGCTTGCCA GAGCCTCCTG GCCGCCGCGG CCGTCTCGAC

1401 TCTGGGCCAC TCTTCACCTT CAAGCTCCTG GGCGATCCTG AGAGCCCGGG

1451 AACCGAAGCG ACAGCCAGCA ACGGGGGCTG CGACACCACG ACCGACCTGG

1501 CCAACGGGCA GCCCGGCTTC AAGAGCAACA TGCCCCTGGG CCCGGGCCAC

1551 TTTTAAAAGC CGAATTC

FIG.15B

1	MetAsnProAspLeuAspThrGlyHisAsn	ThrSerAlaProAlaHisTrpGlyGluLeu	20
21	LysAsnAlaAsnPheThrGlyProAsnGln	ThrSerSerAsnSerThrLeuProGlnLeu	40
41	AspIleThrArgAlaIleSerValGlyLeu	ValLeuGlyAlaPheIleLeuPheAlaIle	60
61	ValGlyAsnIleLeuValIleLeuSerVal	AlaCysAsnArgHisLeuArgThrProThr	80
81	AsnTyrPheIleValAsnLeuAlaMetAla	AspLeuLeuLeuSerPheThrValLeuPro	100
101	PheSerAlaAlaLeuGluValLeuGlyTyr	TrpValLeuGlyArgIlePheCysAspIle	120
121	TrpAlaAlaValAspValLeuCysCysThr	AlaSerIleLeuSerLeuCysAlaIleSer	140
141	IleAspArgTyrIleGlyValArgTyrSer	LeuGlnTyrProThrLeuValThrArgArg	160
161	LysAlaIleLeuAlaLeuLeuSerValTrp	ValLeuSerThrValIleSerIleGlyPro	180
181	LeuLeuGlyTrpLysGluProAlaProAsn	AspAspLysGluCysGlyValThrGluGlu	200
201	ProPheTyrAlaLeuPheSerSerLeuGly	SerPheTyrIleProLeuAlaValIleLeu	220
221	ValMetTyrCysArgValTyrIleValAla	LysArgThrThrLysAsnLeuGluAlaGly	240
241	ValMetLysGluMetSerAsnSerLysGlu	LeuThrLeuArgIleHisSerLysAsnPhe	260
261	HisGluAspThrLeuSerSerThrLysAla	LysGlyHisAsnProArgSerSerIleAla	280
281	ValLysLeuPheLysPheSerArgGluLys	LysAlaAlaLysThrLeuGlyIleValVal	300
301	GlyMetPheIleLeuCysTrpLeuProPhe	PheIleAlaLeuProLeuGlySerLeuPhe	320
321	SerThrLeuLysProProAspAlaValPhe	LysValValPheTrpLeuGlyTyrPheAsn	340
341	SerCysLeuAsnProIleIleTyrProCys	SerSerLysGluPheLysArgAlaPheMet	360
361	ArgIleLeuGlyCysGlnCysArgGlyGly	ArgArgArgArgArgArgArgArgLeuGly	380
381	AlaCysAlaTyrThrTyrArgProTrpThr	ArgGlyGlySerLeuGluArgSerGlnSer	400

FIG.16A

401 ArgLysAspSerLeuAspAspSerGlySer CysMetSerGlyGlnLysArgThrLeuPro 420

421 SerAlaSerProSerProGlyTyrLeuGly ArgGlyThrGlnProProValGluLeuCys 440

441 AlaPheProGluTrpLysProGlyAlaLeu LeuSerLeuProGluProProGlyArgArg 460

461 GlyArgLeuAspSerGlyProLeuPheThr PheLysLeuLeuGlyAspProGluSerPro 480

481 GlyThrGluAlaThrAlaSerAsnGlyGly CysAspThrThrThrAspLeuAlaAsnGly 500

501 GlnProGlyPheLysSerAsnMetProLeu GlyProGlyHisPhe

FIG.16B

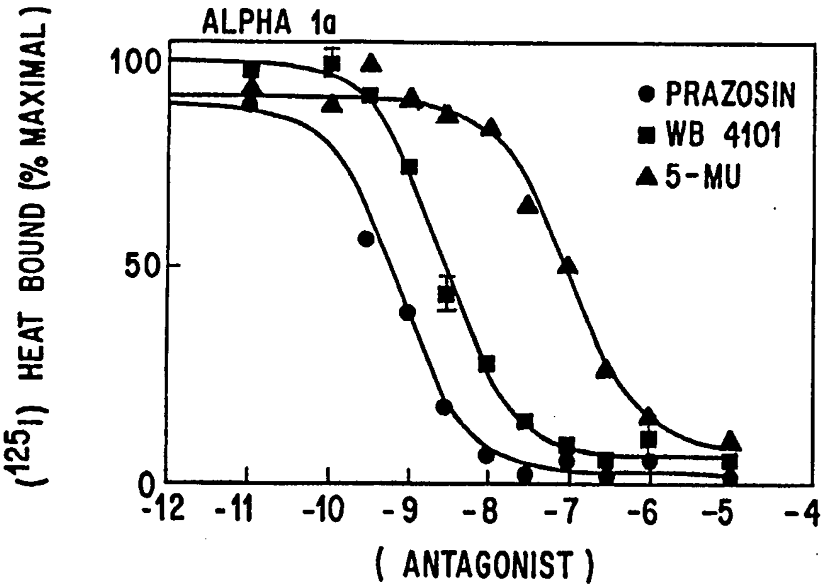


FIG. 17A

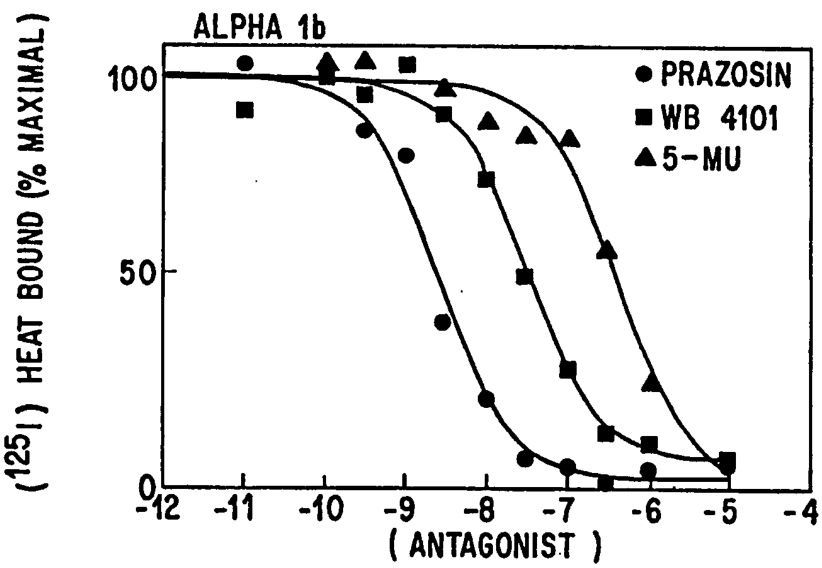


FIG. 17B

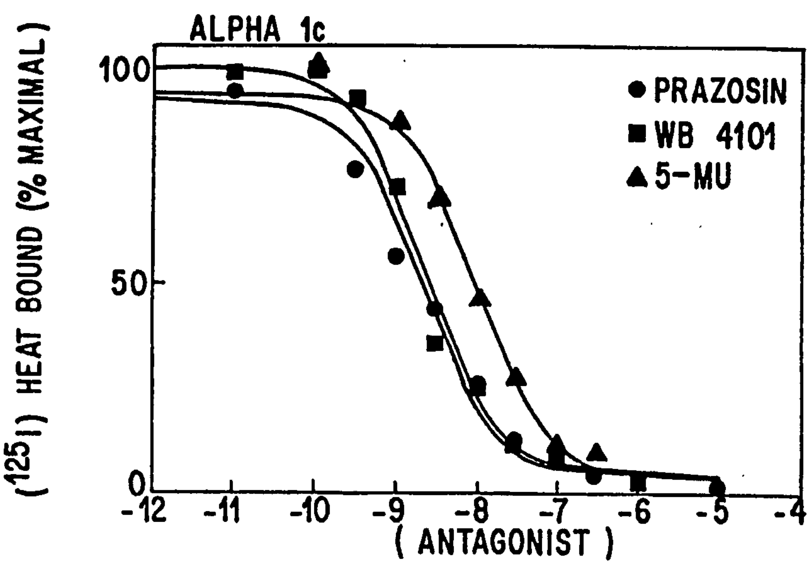


FIG. 17C

1 GAATTCCCTC CTAGAAGCTG GAGAGAGCAG GAGCCTTCGG TGGGGCAGCT

51 CAAAATGTAG GTAACTGCGG GCCAGGAGCA GCGCCCAGAT GCCATCGGTC

101 CCTGCCTTTG AGCGTCGACG GCTGATCTTT TGGTTTGAGG GAGAGACTGG

151 CGCTGGAGTT TTGAATTCCG AATCATGTGC AGAATCGTGA ATCTTCCCCC

201 AGCCAGGACG AATAAGACAG CGCGGAAAAG CAGATTCTCG TAATTCTGGA

251 ATTGCATGTT GCAAGGAGTC TCCTGGATCT TCGCACCCAG CTTCGGGTAC

301 GGGAGGGAGT CCGGGTCCCG GCTAGGCCAG CCCGCAGGTG GAGAGGGTCC

351 CCGGCAGCCC CGCGCGCCCC TGGCCATGTC TTTAATGCCC TGCCCCTTCA

401 TGTGGCCTTC TGAGGGTTCC CAGGGCTGGC CAGGGTTGTC TCCCACCCGC

451 GCGCGCCGTC TCACCCCCAG CCAAACCCAC CTGGCAGGGC TCCCTCCAGA

501 AGAGACCTTT TGATTCCCGG CTCCCGCGCT CCCGCCTCCG CGCCAGCCCG

551 GGAGGTGGCC CTGGACAGCC GGACCTCGCC CGGCCCCGGC TGNGGACCAT

601 GGTGTTTCTC TCGGGAAATG CTTCCGACAG CTCCAACTGC ACCCAACCGC

651 CGGCACCGGT GAACATTTCC AAGGCCATTC TGCTCGGGGT GATCTTGGGG

701 GGCCTCATTC TTTTCGGGGT GCTGGGTAAC ATCCTAGTGA TCCTCTCCGT

751 AGCCTGTCAC CGACACCTGC ACTCAGTCAC GCACTACTAC ATCGTCAACC

801 TGGCGGTGGC CGACCTCCTG CTCACCTCCA CGGTGCTGCC CTTCTCCGCC

851 ATCTTCGAGG TCCTAGGCTA CTGGGCCTTC GGCAGGGTCT TCTGCAACAT

901 CTGGGCGGCA GTGGATGTGC TGTGCTGCAC CGCGTCCATC ATGGGCCTCT

951 GCATCATCTC CATCGACCGC TACATCGGCG TGAGCTACCC GCTGCGCTAC

FIG.18A

1001 CCAACCATCG TCACCCAGAG GAGGGGTCTC ATGGCTCTGC TCTGCGTCTG

1051 GGCACTCTCC CTGGTCATAT CCATTGGACC CCTCTTCGGC TGGAGGCAGC

1101 CGGCCCCCGA GGACGAGACC ATCTGCCAGA TCAACGAGGA GCCGGGCTAC

1151 GTGCTCTTCT CGGCTCTGGG CTCCTTCTAC CTGCCTCTGG CCATCATCCT

1201 GGTCATGTAC TGCCGCGTCT ACGTGGTGGC CAAGAGGGAG AGCCGGGGCC

1251 TCAAGTCTGG CCTCAAGACC GACAAGTCGG ACTCGGAGCA AGTGACGCTC

1301 CGCATCCATC GGAAAAACGC CCCGGCAGGA GGCAGCGGGA TGGCCAGCGC

1351 CAAGACCAAG ACGCACTTCT CAGTGAGGCT CCTCAAGTTC TCCCGGGAGA

1401 AGAAAGCGGC CAAAACGCTG GGCATCGTGG TCGGCTGCTT CGTCCTCTGC

1451 TGGCTGCCTT TTTTCTTAGT CATGCCCATT GGGTCTTTCT TCCCTGATTT

1501 CAAGCCCTCT GAAACAGTTT TTAAAATAGT ATTTTGGCTC GGATATCTAA

1551 ACAGCTGCAT CAACCCCATC ATATACCCAT GCTCCAGCCA AGAGTTCAAA

1601 AAGGCCTTTC AGAATGTCTT GAGAATCCAG TGTCTCCGCA GAAAGCAGTC

1651 TTCCAAACAT GCCCTGGGCT ACACCCTGCA CCCGCCCAGC CAGGCCGTGG

1701 AAGGGCAACA CAAGGACATG GTGCGCATCC CCGTGGGATC AAGAGAGACC

1751 TTCTACAGGA TCTCCAAGAC GGATGGCGTT TGTGAATGGA AATTTTTCTC

1801 TTCCATGCCC CGTGGATCTG CCAGGATTAC AGTGTCCAAA GACCAATCCT

1851 CCTGTACCAC AGCCCGGGTG AGAAGTAAAA GCTTTTTGCA GGTCTGCTGC

1901 TGTGTAGGGC CCTCAACCCC CAGCCTTGAC AAGAACCATC AAGTTCCAAC

1951 CATTAAGGTC CACACCATCT CCCTCAGT

FIG.18B

1	AAT TCC CTC CTA GAA GCT GGA GAG AGC AGG AGC CTT CGG TGG GGC	45
46	AGC TCA AAA TGT AGG TAA CTG CGG GCC AGG AGC AGC GCC CAG ATG	90
91	CCA TCG GTC CCT GCC TTT GAG CGT CGA CGG CTG ATC TTT TGG TTT	135
136	GAG GGA GAG ACT GGC GCT GGA GTT TTG AAT TCC GAA TCA TGT GCA	180
181	GAA TCG TGA ATC TTC CCC CAG CCA GGA CGA ATA AGA CAG CGC GGA	225
226	AAA GCA GAT TCT CGT AAT TCT GGA ATT GCA TGT TGC AAG GAG TCT	270
271	CCT GGA TCT TCG CAC CCA GCT TCG GGT ACG GGA GGG AGT CCG GGT	315
316	CCC GGC TAG GCC AGC CCG CAG GTG GAG AGG GTC CCC GGC AGC CCC	360
361	GCG CGC CCC TGG CCA TGT CTT TAA TGC CCT GCC CCT TCA TGT GGC	405
406	CTT CTG AGG GTT CCC AGG GCT GGC CAG GGT TGT CTC CCA CCC GCG	450
451	CGC GCC GTC TCA CCC CCA GCC AAA CCC ACC TGG CAG GGC TCC CTC	495
496	CAG AAG AGA CCT TTT GAT TCC CGG CTC CCG CGC TCC CGC CTC CGC	540
541	GCC AGC CCG GGA GGT GGC CCT GGA CAG CCG GAC CTC GCC CGG CCC	585
586	CGG CTG NGG ACC ATG GTG TTT CTC TCG GGA AAT GCT TCC GAC AGC	630
631	TCC AAC TGC ACC CAA CCG CCG GCA CCG GTG AAC ATT TCC AAG GCC	675
676	ATT CTG CTC GGG GTG ATC TTG GGG GGC CTC ATT CTT TTC GGG GTG	720
721	CTG GGT AAC ATC CTA GTG ATC CTC TCC GTA GCC TGT CAC CGA CAC	765
766	CTG CAC TCA GTC ACG CAC TAC TAC ATC GTC AAC CTG GCG GTG GCC	810
811	GAC CTC CTG CTC ACC TCC ACG GTG CTG CCC TTC TCC GCC ATC TTC	855
856	GAG GTC CTA GGC TAC TGG GCC TTC GGC AGG GTC TTC TGC AAC ATC	900

FIG.19A

901 TGG GCG GCA GTG GAT GTG CTG TGC TGC ACC GCG TCC ATC ATG GGC 945

946 CTC TGC ATC ATC TCC ATC GAC CGC TAC ATC GGC GTG AGC TAC CCG 990

991 CTG CGC TAC CCA ACC ATC GTC ACC CAG AGG AGG GGT CTC ATG GCT 1035

1036 CTG CTC TGC GTC TGG GCA CTC TCC CTG GTC ATA TCC ATT GGA CCC 1080

1081 CTC TTC GGC TGG AGG CAG CCG GCC CCC GAG GAC GAG ACC ATC TGC 1125

1126 CAG ATC AAC GAG GAG CCG GGC TAC GTG CTC TTC TCG GCT CTG GGC 1170

1171 TCC TTC TAC CTG CCT CTG GCC ATC ATC CTG GTC ATG TAC TGC CGC 1215

1216 GTC TAC GTG GTG GCC AAG AGG GAG AGC CGG GGC CTC AAG TCT GGC 1260

1261 CTC AAG ACC GAC AAG TCG GAC TCG GAG CAA GTG ACG CTC CGC ATC 1305

1306 CAT CGG AAA AAC GCC CCG GCA GGA GGC AGC GGG ATG GCC AGC GCC 1350

1351 AAG ACC AAG ACG CAC TTC TCA GTG AGG CTC CTC AAG TTC TCC CGG 1395

1396 GAG AAG AAA GCG GCC AAA ACG CTG GGC ATC GTG GTC GGC TGC TTC 1440

1441 GTC CTC TGC TGG CTG CCT TTT TTC TTA GTC ATG CCC ATT GGG TCT 1485

1486 TTC TTC CCT GAT TTC AAG CCC TCT GAA ACA GTT TTT AAA ATA GTA 1530

1531 TTT TGG CTC GGA TAT CTA AAC AGC TGC ATC AAC CCC ATC ATA TAC 1575

1576 CCA TGC TCC AGC CAA GAG TTC AAA AAG GCC TTT CAG AAT GTC TTG 1620

1621 AGA ATC CAG TGT CTC TGC AGA AAG CAG TCT TCC AAA CAT GCC CTG 1665

1666 GGC TAC ACC CTG CAC CCG CCC AGC CAG GCC GTG GAA GGG CAA CAC 1710

1711 AAG GAC ATG GTG CGC ATC CCC GTG GGA TCA AGA GAG ACC TTC TAC 1755

FIG.19B

1756	AGG ATC TCC AAG ACG GAT GGC GTT TGT GAA TGG AAA TTT TTC TCT	1800
1801	TCC ATG CCC CGT GGA TCT GCC AGG ATT ACA GTG TCC AAA GAC CAA	1845
1846	TCC TCC TGT ACC ACA GCC CGG GTG AGA AGT AAA AGC TTT TTG CAG	1890
1891	GTC TGC TGC TGT GTA GGG CCC TCA ACC CCC AGC CTT GAC AAG AAC	1935
1936	CAT CAA GTT CCA ACC ATT AAG GTC CAC ACC ATC TCC CTC AGT GAG	1980
1981	AAC GGG GAG GAA GTC TAG	1998

FIG.19C

1 Met Val Phe Leu Ser Gly Asn Ala Ser Asp Ser Ser Asn Cys Thr
Gln Pro Pro Ala Pro Val Asn Ile Ser Lys Ala 26
27 Ile Leu Leu Gly Val Ile Leu Gly Gly Leu Ile Leu Phe Gly Val 41
42 Leu Gly Asn Ile Leu Val Ile Leu Ser Val Ala Cys His Arg His 56
57 Leu His Ser Val Thr His Tyr Tyr Ile Val Asn Leu Ala Val Ala 71
72 Asp Leu Leu Leu Thr Ser Thr Val Leu Pro Phe Ser Ala Ile Phe 86
87 Glu Val Leu Gly Tyr Trp Ala Phe Gly Arg Val Phe Cys Asn Ile 101
102 Trp Ala Ala Val Asp Val Leu Cys Cys Thr Ala Ser Ile Met Gly 116
946 ctc tgc atc atc tcc atc gac cgc tac atc ggc gtg agc tac cCg 990
117 Leu Cys Ile Ile Ser Ile Asp Arg Tyr Ile Gly Val Ser Tyr Pro 131
132 Leu Arg Tyr Pro Thr Ile Val Thr Gln Arg Arg Gly Leu Met Ala 146
147 Leu Leu Cys Val Trp Ala Leu Ser Leu Val Ile Ser Ile Gly Pro 161
162 Leu Phe Gly Trp Arg Gln Pro Ala Pro Glu Asp Glu Thr Ile Cys 176
177 Gln Ile Asn Glu Glu Pro Gly Tyr Val Leu Phe Ser Ala Leu Gly 191
192 Ser Phe Tyr Leu Pro Leu Ala Ile Ile Leu Val Met Tyr Cys Arg 206
207 Val Tyr Val Val Ala Lys Arg Glu Ser Arg Gly Leu Lys Ser Gly 221
222 Leu Lys Thr Asp Lys Ser Asp Ser Glu Gln Val Thr Leu Arg Ile 236
237 His Arg Lys Asn Ala Pro Ala Gly Gly Ser Gly Met Ala Ser Ala 251
252 Lys Thr Lys Thr His Phe Ser Val Arg Leu Leu Lys Phe Ser Arg 266
267 Glu Lys Lys Ala Ala Lys Thr Leu Gly Ile Val Val Gly Cys Phe 281
282 Val Leu Cys Trp Leu Pro Phe Phe Leu Val Met Pro Ile Gly Ser 296
297 Phe Phe Pro Asp Phe Lys Pro Ser Glu Thr Val Phe Lys Ile Val 311
312 Phe Trp Leu Gly Tyr Leu Asn Ser Cys Ile Asn Pro Ile Ile Tyr 326
327 Pro Cys Ser Ser Gln Glu Phe Lys Lys Ala Phe Gln Asn Val Leu 341
342 Arg Ile Gln Cys Leu CYS Arg Lys Gln Ser Ser Lys His Ala Leu 356
357 Gly Tyr Thr Leu His Pro Pro Ser Gln Ala Val Glu Gly Gln His 371
372 Lys Asp Met Val Arg Ile Pro Val Gly Ser Arg Glu Thr Phe Tyr 386
387 Arg Ile Ser Lys Thr Asp Gly Val Cys Glu Trp Lys Phe Phe Ser 401
402 Ser Met Pro Arg Gly Ser Ala Arg Ile Thr Val Ser Lys Asp Gln 416
417 Ser Ser Cys Thr Thr Ala Arg Val Arg Ser Lys Ser Phe Leu Gln 431
432 Val Cys Cys Cys Val Gly Pro Ser Thr Pro Ser Leu Asp Lys Asn 446
447 His Gln Val Pro Thr Ile Lys Val His Thr Ile Ser Leu Ser Glu 461
462 Asn Gly Glu Glu Val End 466

FIG.20

1 AAT TCC CTC CTA GAA GCT GGA GAG AGC AGG AGC CTT CGG TGG GGC 45

46 AGC TCA AAA TGT AGG TAA CTG CGG GCC AGG AGC AGC GCC CAG ATG 90

91 CCA TCG GTC CCT GCC TTT GAG CGT CGA CGG CTG ATC TTT TGG TTT 135

136 GAG GGA GAG ACT GGC GCT GGA GTT TTG AAT TCC GAA TCA TGT GCA 180

181 GAA TCG TGA ATC TTC CCC CAG CCA GGA CGA ATA AGA CAG CGC GGA 225

226 AAA GCA GAT TCT CGT AAT TCT GGA ATT GCA TGT TGC AAG GAG TCT 270

271 CCT GGA TCT TCG CAC CcA GCT TCG GgT aCG GgA GGg AGT CcG GgT 315

316 CCc GGC TAG GCc AGC ccg cag gtg gag agg gtc ccc ggc agc ccc 360

361 GCG CGC CCC TGG CCA TGT CTT TAA TGC CCT GCC CCT TCA TGT GGC 405

406 CTT CTG AGG GTT CCC AGG GCT GGC CAG GGT TGT CTC CCA CCC GCG 450

451 CGC GCC GTC TCA CCC CCA GCC AAA CCC ACC TGG CAG GGC TCC CTC 495

496 CAG AAG AGA CCT TTT GAT TCC CGG CTC CCG CGC TCC CGC CTC CGC 540

541 GCC AGC CCG GGA GGT GGC CCT GGA CAG CCG GAC CTC GCC CGG CCC 585

586 CGG CTG NGG ACC ATG GTG TTT CTC TCG GGA AAT GCT TCC GAC AGC 630
1 Met Val Phe Leu Ser Gly Asn Ala Ser Asp Ser 11

631 TCC AAC TGC ACC CAA CCG CCG GCA CCG GTG AAC ATT TCC AAG GCC 675
12 Ser Asn Cys Thr Gln Pro Pro Ala Pro Val Asn Ile Ser Lys Ala 26

676 ATT CTG CTC GGG GTG ATC TTG GGG GGC CTC ATT CTT TTC GGG GTG 720
27 Ile Leu Leu Gly Val Ile Leu Gly Gly Leu Ile Leu Phe Gly Val 41

721 CTG GGT AAC ATC CTA GTG ATC CTC TCC GTA GCC TGT CAC CGA CAC 765
42 Leu Gly Asn Ile Leu Val Ile Leu Ser Val Ala Cys His Arg His 56

FIG.21A

766 CTG CAC TCA GTC ACG CAC TAC TAC ATC GTC AAC CTG GCG GTG GCC 810
57 Leu His Ser Val Thr His Tyr Tyr Ile Val Asn Leu Ala Val Ala 71

811 GAC CTC CTG CTC ACC TCC ACG GTG CTG CCC TTC TCC GCC ATC TTC 855
72 Asp Leu Leu Leu Thr Ser Thr Val Leu Pro Phe Ser Ala Ile Phe 86

856 GAG GTC CTA GGC TAC TGG GCC TTC GGC AGG GTC TTC TGC AAC ATC 900
87 Glu Val Leu Gly Tyr Trp Ala Phe Gly Arg Val Phe Cys Asn Ile 101

901 TGG GCG GCA GTG GAT GTG CTG TGC TGC ACC GCG TCC ATC ATG GGC 945
102 Trp Ala Ala Val Asp Val Leu Cys Cys Thr Ala Ser Ile Met Gly 116

946 CTC TGC ATC ATC TCC ATC GAC CGC TAC ATC GGC GTG AGC TAC CCG 990
117 Leu Cys Ile Ile Ser Ile Asp Arg Tyr Ile Gly Val Ser Tyr Pro 131

991 CTG CGC TAC CCA ACC ATC GTC ACC CAG AGG AGG GGT CTC ATG GCT 1035
132 Leu Arg Tyr Pro Thr Ile Val Thr Gln Arg Arg Gly Leu Met Ala 146

1036 CTG CTC TGC GTC TGG GCA CTC TCC CTG GTC ATA TCC ATT GGA CCC 1080
147 Leu Leu Cys Val Trp Ala Leu Ser Leu Val Ile Ser Ile Gly Pro 161

1081 CTC TTC GGC TGG AGG CAG CCG GCC CCC GAG GAC GAG ACC ATC TGC 1125
162 Leu Phe Gly Trp Arg Gln Pro Ala Pro Glu Asp Glu Thr Ile Cys 176

1126 CAG ATC AAC GAG GAG CCG GGC TAC GTG CTC TTC TCG GCT CTG GGC 1170
177 Gln Ile Asn Glu Glu Pro Gly Tyr Val Leu Phe Ser Ala Leu Gly 191

1171 TCC TTC TAC CTG CCT CTG GCC ATC ATC CTG GTC ATG TAC TGC CGC 1215
192 Ser Phe Tyr Leu Pro Leu Ala Ile Ile Leu Val Met Tyr Cys Arg 206

1216 GTC TAC GTG GTG GCC AAG AGG GAG AGC CGG GGC CTC AAG TCT GGC 1260
207 Val Tyr Val Val Ala Lys Arg Glu Ser Arg Gly Leu Lys Ser Gly 221

1261 CTC AAG ACC GAC AAG TCG GAC TCG GAG CAA GTG ACG CTC CGC ATC 1305
222 Leu Lys Thr Asp Lys Ser Asp Ser Glu Gln Val Thr Leu Arg Ile 236

1306 CAT CGG AAA AAC GCC CCG GCA GGA GGC AGC GGG ATG GCC AGC GCC 1350
237 His Arg Lys Asn Ala Pro Ala Gly Gly Ser Gly Met Ala Ser Ala 251

1351 AAG ACC AAG ACG CAC TTC TCA GTG AGG CTC CTC AAG TTC TCC CGG 1395
252 Lys Thr Lys Thr His Phe Ser Val Arg Leu Leu Lys Phe Ser Arg 266

FIG.21B

1396	GAG AAG AAA GCG GCC AAA ACG CTG GGC ATC GTG GTC GGC TGC TTC	1440
267	Glu Lys Lys Ala Ala Lys Thr Leu Gly Ile Val Val Gly Cys Phe	281
1441	GTC CTC TGC TGG CTG CCT TTT TTC TTA GTC ATG CCC ATT GGG TCT	1485
282	Val Leu Cys Trp Leu Pro Phe Phe Leu Val Met Pro Ile Gly Ser	296
1486	TTC TTC CCT GAT TTC AAG CCC TCT GAA ACA GTT TTT AAA ATA GTA	1530
297	Phe Phe Pro Asp Phe Lys Pro Ser Glu Thr Val Phe Lys Ile Val	311
1531	TTT TGG CTC GGA TAT CTA AAC AGC TGC ATC AAC CCC ATC ATA TAC	1575
312	Phe Trp Leu Gly Tyr Leu Asn Ser Cys Ile Asn Pro Ile Ile Tyr	326
1576	CCA TGC TCC AGC CAA GAG TTC AAA AAG GCC TTT CAG AAT GTC TTG	1620
327	Pro Cys Ser Ser Gln Glu Phe Lys Lys Ala Phe Gln Asn Val Leu	341
1621	AGA ATC CAG TGT CTC TGC AGA AAG CAG TCT TCC AAA CAT GCC CTG	1665
342	Arg Ile Gln Cys Leu CYS Arg Lys Gln Ser Ser Lys His Ala Leu	356
1666	GGC TAC ACC CTG CAC CCG CCC AGC CAG GCC GTG GAA GGG CAA CAC	1710
357	Gly Tyr Thr Leu His Pro Pro Ser Gln Ala Val Glu Gly Gln His	371
1711	AAG GAC ATG GTG CGC ATC CCC GTG GGA TCA AGA GAG ACC TTC TAC	1755
372	Lys Asp Met Val Arg Ile Pro Val Gly Ser Arg Glu Thr Phe Tyr	386
1756	AGG ATC TCC AAG ACG GAT GGC GTT TGT GAA TGG AAA TTT TTC TCT	1800
387	Arg Ile Ser Lys Thr Asp Gly Val Cys Glu Trp Lys Phe Phe Ser	401
1801	TCC ATG CCC CGT GGA TCT GCC AGG ATT ACA GTG TCC AAA GAC CAA	1845
402	Ser Met Pro Arg Gly Ser Ala Arg Ile Thr Val Ser Lys Asp Gln	416
1846	TCC TCC TGT ACC ACA GCC CGG GTG AGA AGT AAA AGC TTT TTG CAG	1890
417	Ser Ser Cys Thr Thr Ala Arg Val Arg Ser Lys Ser Phe Leu Gln	431
1891	GTC TGC TGC TGT GTA GGG CCC TCA ACC CCC AGC CTT GAC AAG AAC	1935
432	Val Cys Cys Cys Val Gly Pro Ser Thr Pro Ser Leu Asp Lys Asn	446
1936	CAT CAA GTT CCA ACC ATT AAG GTC CAC ACC ATC TCC CTC AGT GAG	1980
447	His Gln Val Pro Thr Ile Lys Val His Thr Ile Ser Leu Ser Glu	461
1981	AAC GGG GAG GAA GTC TAG	1998
462	Asn Gly Glu Glu Val End	466

FIG.21C

-57
CTCCCTGCCG GCCGCTCGTT CTGTGCCCCG GCCCGGCCAC CGACGGCCGG CGTTGAG ATGACT 6

TTC CGC GAT CTC CTG AGC GTC AGT TTC GAG GGA CCC CGC CCG GAC AGC AGCGCA 60

GGG GGC TCC AGC GCG GGC GGC GGC GGG GGC GGC GCG GGC GGC GCG GCC CCCTCG 114

GAG GGC CCG GCG GTG GGC GGC GTG CCG GGG GGC GCG GGC GGC GGC GGC GGCGTG 168

GTG GGC GCA GGC AGC GGC GAG GAC AAC CGG AGC TCC GCG GGG GAG CCG GGGAGC 222

GCG GGC GCG GGC GGC GAC GTG AAT GGC ACG GCG GCC GTC GGG GGA CTG GTGGTG 276

AGC GCG CAG GGC GTG GGC GTG GGC GTC TTC CTG GCA GCC TTC ATC CTT ATGGCC 330

GTG GCA GGT AAC CTG CTT GTC ATC CTC TCA GTG GCC TGC AAC CGC CAC CTGCAG 384

ACC GTC ACC AAC TAT TTC ATC GTG AAC CTG GCC GTG GCC GAC CTG CTG CTGAGC 438

GCC ACC GTA CTG CCC TTC TCG GCC ACC ATG GAG GTT CTG GGC TTC TGG GCCTTT 492

GGC CGC GCC TTC TGC GAC GTA TGG GCC GCC GTG GAC GTG CTG TGC TGC ACGGCC 546

TCC ATC CTC AGC CTC TGC ACC ATC TCC GTG GAC CGG TAC GTG GGC GTG CGCCAC 600

TCA CTC AAG TAC CCA GCC ATC ATG ACC GAG CGC AAG GCG GCC GCC ATC CTGGCC 654

CTG CTC TGG GTC GTA GCC CTG GTG GTG TCC GTA GGG CCC CTG CTG GGC TGGAAG 708

GAG CCC GTG CCC CCT GAC GAG CGC TTC TGC GGT ATC ACC GAG GAG GCG GGCTAC 762

GCT GTC TTC TCC TCC GTG TGC TCC TTC TAC CTG CCC ATG GCG GTC ATC GTGGTC 816

ATG TAC TGC CGC GTG TAC GTG GTC GCG CGC AGC ACC ACG CGC AGC CTC GAGGCG 870

GGC GTC AAG CGC GAG CGA GGC AAG GCC TCC GAG GTG GTG CTG CGC ATC CACTGT 924

FIG.22A

CGC GGC GCG GCC ACG GGC GCC GAC GGG GCG CAC GGC ATG CGC AGC GCC AAGGGC 978

CAC ACC TTC CGC AGC TCG CTC TCC GTG CGC CTG CTC AAG TTC TCC CGT GAGAAG 1032

AAA GCG GCC AAG ACT CTG GCC ATC GTC GTG GGT GTC TTC GTG CTC TGC TGGTTC 1086

CCT TTC TTC TTT GTC CTG CCG CTC GGC TCC TTG TTC CCG CAG CTG AAG CCATCG 1140

GAG GGC GTC TTC AAG GTC ATC TTC TGG CTC GGC TAC TTC AAC AGC TGC GTGAAC 1194

CCG CTC ATC TAC CCC TGT TCC AGC CGC GAG TTC AAG CGC GCC TTC CTC CGTCTC 1248

CTG CGC TGC CAG TGC CGT CGT CGC CGG CGC CGC CGC CCT CTC TGG CGT GTCTAC 1302

GGC CAC CAC TGG CGG GCC TCC ACC AGC GGC CTG CGC CAG GAC TGC GCC CCGAGT 1356

TCG GGC GAC GCG CCC CCC GGA GCG CCG CTG GCC CTC ACC GCG CTC CCC GACCCC 1410

GAC CCC GAA CCC CCA GGC ACG CCC GAG ATG CAG GCT CCG GTC GCC AGC CGTCGA 1464

AAG CCA CCC AGC GCC TTC CGC GAG TGG AGG CTG CTG GGG CCG TTC CGG AGACCC 1518

ACG ACC CAG CTG CGC GCC AAA GTC TCC AGC CTG TCG CAC AAG ATC CGC GCCGGG 1572

GGC GCG CAG CGC GCA GAG GCA GCG TGC GCC CAG CGC TCA GAG GTG GAG GCTGTG 1626

TCC CTA GGC GTC CCA CAC GAG GTG GCC GAG GGC GCC ACC TGC CAG GCC TACGAA 1680

TTG GCC GAC TAC AGC AAC CTA CGG GAG ACC GAT ATT TAA 1719

FIG.22B

																M	T
F	R	D	L	L	S	V	S	F	E	G	P	R	P	D	S	S	A
G	G	S	S	A	G	G	G	G	G	G	A	G	G	A	A	P	S
E	G	P	A	V	G	G	V	P	G	G	A	G	G	G	G	G	V
V	G	A	G	S	G	E	D	N	R	S	S	A	G	E	P	G	S
A	G	A	G	G	D	V	N	G	T	A	A	V	G	G	L	V	V
S	A	Q	G	V	G	V	G	V	F	L	A	A	F	I	L	M	A
V	A	G	N	L	L	V	I	L	S	V	A	C	N	R	H	L	Q
T	V	T	N	Y	F	I	V	N	L	A	V	A	D	L	L	L	S
A	T	V	L	P	F	S	A	T	M	E	V	L	G	F	W	A	F
G	R	A	F	C	D	V	W	A	A	V	D	V	L	C	C	T	A
S	I	L	S	L	C	T	I	S	V	D	R	Y	V	G	V	R	H
S	L	K	Y	P	A	I	M	T	E	R	K	A	A	A	I	L	A
L	L	W	V	V	A	L	V	V	S	V	G	P	L	L	G	W	K
E	P	V	P	P	D	E	R	F	C	G	I	T	E	E	A	G	Y
A	V	F	S	S	V	C	S	F	Y	L	P	M	A	V	I	V	V
M	Y	C	R	V	Y	V	V	A	R	S	T	T	R	S	L	E	A
G	V	K	R	E	R	G	K	A	S	E	V	V	L	R	I	H	C
R	G	A	A	T	G	A	D	G	A	H	G	M	R	S	A	K	G
H	T	F	R	S	S	L	S	V	R	L	L	K	F	S	R	E	K
K	A	A	K	T	L	A	I	V	V	G	V	F	V	L	C	W	F
P	F	F	F	V	L	P	L	G	S	L	F	P	Q	L	K	P	S
E	G	V	F	K	V	I	F	W	L	G	Y	F	N	S	C	V	N
P	L	I	Y	P	C	S	S	R	E	F	K	R	A	F	L	R	L
L	R	C	Q	C	R	R	R	R	R	R	R	P	L	W	R	V	Y
G	H	H	W	R	A	S	T	S	G	L	R	Q	D	C	A	P	S
S	G	D	A	P	P	G	A	P	L	A	L	T	A	L	P	D	P
D	P	E	P	P	G	T	P	E	M	Q	A	P	V	A	S	R	R
K	P	P	S	A	F	R	E	W	R	L	L	G	P	F	R	R	P
T	T	Q	L	R	A	K	V	S	S	L	S	H	K	I	R	A	G
G	A	Q	R	A	E	A	A	C	A	Q	R	S	E	V	E	A	V
S	L	G	V	P	H	E	V	A	E	G	A	T	C	Q	A	Y	E
L	A	D	Y	S	N	L	R	E	T	D	I	.					

FIG.23

-57 >
CTCCCTGCCG GCCGCTCGTT CTGTGCCCCG GCCCGGCCAC CGACGGCCGG CGTTGAG ATG ACT 6
M T

TTC CGC GAT CTC CTG AGC GTC AGT TTC GAG GGA CCC CGC CCG GAC AGC AGC GCA 60
F R D L L S V S F E G P R P D S S A

GGG GGC TCC AGC GCG GGC GGC GGC GGG GGC GGC GCG GGC GGC GCG GCC CCC TCG 114
G G S S A G G G G G G A G G A A P S

GAG GGC CCG GCG GTG GGC GGC GTG CCG GGG GGC GCG GGC GGC GGC GGC GGC GTG 168
E G P A V G G V P G G A G G G G G V

GTG GGC GCA GGC AGC GGC GAG GAC AAC CGG AGC TCC GCG GGG GAG CCG GGG AGC 222
V G A G S G E D N R S S A G E P G S
*

GCG GGC GCG GGC GGC GAC GTG AAT GGC ACG GCG GCC GTC GGG GGA CTG GTG GTG 276
A G A G G D V N G T A A V G G L V V
*

AGC GCG CAG GGC GTG GGC GTG GGC GTC TTC CTG GCA GCC TTC ATC CTT ATG GCC 330
S A Q G V G V G V F L A A F I L M A

GTG GCA GGT AAC CTG CTT GTC ATC CTC TCA GTG GCC TGC AAC CGC CAC CTG CAG 384
V A G N L L V I L S V A C N R H L Q

FIG.24A

ACC GTC ACC AAC TAT TTC ATC GTG AAC CTG GCC GTG GCC GAC CTG CTG CTG AGC 438
T V T N Y F I V N L A V A D L L L S

GCC ACC GTA CTG CCC TTC TCG GCC ACC ATG GAG GTT CTG GGC TTC TGG GCC TTT 492
A T V L P F S A T M E V L G F W A F

GGC CGC GCC TTC TGC GAC GTA TGG GCC GCC GTG GAC GTG CTG TGC TGC ACG GCC 546
G R A F C D V W A A V D V L C C T A

TCC ATC CTC AGC CTC TGC ACC ATC TCC GTG GAC CGG TAC GTG GGC GTG CGC CAC 600
S I L S L C T I S V D R Y V G V R H

TCA CTC AAG TAC CCA GCC ATC ATG ACC GAG CGC AAG GCG GCC GCC ATC CTG GCC 654
S L K Y P A I M T E R K A A A I L A

CTG CTC TGG GTC GTA GCC CTG GTG GTG TCC GTA GGG CCC CTG CTG GGC TGG AAG 708
L L W V V A L V V S V G P L L G W K

GAG CCC GTG CCC CCT GAC GAG CGC TTC TGC GGT ATC ACC GAG GAG GCG GGC TAC 762
E P V P P D E R F C G I T E E A G Y

GCT GTC TTC TCC TCC GTG TGC TCC TTC TAC CTG CCC ATG GCG GTC ATC GTG GTC 816
A V F S S V C S F Y L P M A V I V V

ATG TAC TGC CGC GTG TAC GTG GTC GCG CGC AGC ACC ACG CGC AGC CTC GAG GCG 870
M Y C R V Y V V A R S T T R S L E A

FIG.24B

GGC GTC AAG CGC GAG CGA GGC AAG GCC TCC GAG GTG GTG CTG CGC ATC CAC TGT 924
G V K R E R G K A S E V V L R I H C

CGC GGC GCG GCC ACG GGC GCC GAC GGG GCG CAC GGC ATG CGC AGC GCC AAG GGC 978
R G A A T G A D G A H G M R S A K G

CAC ACC TTC CGC AGC TCG CTC TCC GTG CGC CTG CTC AAG TTC TCC CGT GAG AAG 1032
H T F R S S L S V R L L K F S R E K

AAA GCG GCC AAG ACT CTG GCC ATC GTC GTG GGT GTC TTC GTG CTC TGC TGG TTC 1086
K A A K T L A I V V G V F V L C W F

CCT TTC TTC TTT GTC CTG CCG CTC GGC TCC TTG TTC CCG CAG CTG AAG CCA TCG 1140
P F F F V L P L G S L F P Q L K P S

GAG GGC GTC TTC AAG GTC ATC TTC TGG CTC GGC TAC TTC AAC AGC TGC GTG AAC 1194
E G V F K V I F W L G Y F N S C V N

CCG CTC ATC TAC CCC TGT TCC AGC CGC GAG TTC AAG CGC GCC TTC CTC CGT CTC 1248
P L I Y P C S S R E F K R A F L R L

CTG CGC TGC CAG TGC CGT CGT CGC CGG CGC CGC CGC CCT CTC TGG CGT GTC TAC 1302
L R C Q C R R R R R R R P L W R V Y

FIG.24C

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GGC CAC CAC TGG CGG GCC TCC ACC AGC GGC CTG CGC CAG GAC TGC GCC CCG AGT   1356
G   H   H   W   R   A   S   T   S   G   L   R   Q   D   C   A   P   S

TCG GGC GAC GCG CCC CCC GGA GCG CCG CTG GCC CTC ACC GCG CTC CCC GAC CCC   1410
S   G   D   A   P   P   G   A   P   L   A   L   T   A   L   P   D   P

GAC CCC GAA CCC CCA GGC ACG CCC GAG ATG CAG GCT CCG GTC GCC AGC CGT CGA   1464
D   P   E   P   P   G   T   P   E   M   Q   A   P   V   A   S   R   R

AAG CCA CCC AGC GCC TTC CGC GAG TGG AGG CTG CTG GGG CCG TTC CGG AGA CCC   1518
K   P   P   S   A   F   R   E   W   R   L   L   G   P   F   R   R   P

ACG ACC CAG CTG CGC GCC AAA GTC TCC AGC CTG TCG CAC AAG ATC CGC GCC GGG   1572
T   T   Q   L   R   A   K   V   S   S   L   S   H   K   I   R   A   G

GGC GCG CAG CGC GCA GAG GCA GCG TGC GCC CAG CGC TCA GAG GTG GAG GCT GTG   1626
G   A   Q   R   A   E   A   A   C   A   Q   R   S   E   V   E   A   V

TCC CTA GGC GTC CCA CAC GAG GTG GCC GAG GGC GCC ACC TGC CAG GCC TAC GAA   1680
S   L   G   V   P   H   E   V   A   E   G   A   T   C   Q   A   Y   E

TTG GCC GAC TAC AGC AAC CTA CGG GAG ACC GAT ATT TAA   1719
L   A   D   Y   S   N   L   R   E   T   D   I   .
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FIG.24D

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US95/04590

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :Please See Extra Sheet.
US CL :Please See Extra Sheet.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/170, 257, 278, 302, 321, 322, 323, 193; 544/283; 546/17, 200, 197, 198, 199, 115, 271; 546/198, 199; 514/321, 322

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

BEILSTEIN, CHEMICAL ABSTRACTS (CA)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FR, A, 2,621,588 (BOAVENTURA ET AL.) 18 OCTOBER 1987, see entire document.	1-7

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date		
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed	"&"	document member of the same patent family

Date of the actual completion of the international search
20 JULY 1995

Date of mailing of the international search report
08 AUG 1995

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Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US95/04590

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-7, 12, 16, 17, 20, and 23-26 (in-part)

Remark on Protest
☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US95/04590

A. CLASSIFICATION OF SUBJECT MATTER:
IPC (6):

C07D 401/04, 413/04, 471/04, 471/10; A61K 31/415, 31/42, 31/445, 31/44, 31/47, 31/505

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

514/170, 257, 278, 302, 321, 322, 323, 193; 544/283; 546/17, 200, 197, 198, 199, 115, 271

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

Invention I:Claims 1-7, 12, 16, 17, 20, and 23-26 in-part drawn to compounds, pharmaceutical compositions and methods of treating benign prostatic hyperplasia wherein the term (X) in the depicted formula(a) represents [4-(2-oxo-3-benzoxazolinyl)], 4-(2-oxo-3-benzthiazolinyl), 4-(1,3-dihydro-2-oxo-benzimidazolin-1-yl) all optionally substituted as defined; the term (E) in the main formula represents carbonyl or sulfonyl, the term (Y) in the main formula represents sulfonyl; the terms (A, B, G, D) in the main formula represent carbon; the terms R1, R2, R3, and R4 and the integer (n) in the main formula are as defined, the term (Q) in main formula represents (CH2)r wherein r is one. This invention is classified in Class 546, subclasses 198 and 199; class 514, subclasses 321 and 322.

Invention II:Claims 1-7, 12, 16, 17, 20, and 23-26 (in-part) drawn to compounds, pharmaceutical compositions, and methods of treating benign prostatic hyperplasia except that the term (X) represents optionally substituted 4-(2-oxo-(1H)quinolin-1-yl) 4-(3,4-dihydro-2-oxo-(1H)quinolin-1-yl) and (4-(1,3-dihydro-2-oxo-(1H)-3,4-dihydro-quinazolin-1-yl) moieties classified in Class 544; subclass 283; Class 546, subclass 200; Class 514, subclasses 257 and 312, respectively.

Invention III:Claims 1-7, 12, 16, 17, 20, and 23-26 (in-part) drawn to compounds, pharmaceutical compositions, and methods of treating benign prostatic hyperplasia except that the term (X) represents 3, 3a, 8, 8a-tetrahydro-2H-indeno [1,2-d]-oxazolinyl or 4-(2-oxo-naphth-[2,3-d]oxazolinyl moieties. This invention is classified in Class 198; Class 514, subclass 321.

Invention IV:Claims 1-7, 12, 16, 17, 20, and 23-26 (in-part), drawn to compounds, pharmaceutical compositions, and methods of treating benign prostatic hyperplasia and Invention I, except that the term (X) represents 4-(2-oxo-3-oxazolo[4,5-b]pyridine). This invention is classified in Class 546, subclass 115; Class 514, subclass 302.

Invention V:Claims 1-7, 12, 16, 17, 20, and 23-26 (in-part) drawn to compounds, pharmaceutical compositions, and methods of treating benign prostatic hyperplasia and except that spiro compounds are involved according to formula (b) of claim one. This invention is classified in Class 546, subclass 17; Class 514, subclass 278.

Invention VI:Claims 1, 2, 12, 16, 17, 20, and 23-26 (in-part) drawn to compounds, pharmaceutical compositions, and methods of treating benign prostatic hyperplasia except that the 1,2-benzoisothiazol-3(2H)one moiety is replaced by a phthalimide ring. Class 546, subclass 271; Class 514, subclass 323.

Invention VII:Claims 1, 2, 12, 16, 17, 20, and 23-26 (in-part) except that it includes all of the residual compounds not previously defined. This invention is classified in plethora of subclasses in Classes 540, 544, 546, 548, and 549.

Invention VIII: Claims 8-11, 13-15, 18, 19, 21, and 22 (in-part) drawn to pharmaceutical compositions and methods of use comprising a compound according to Inventions I-IV and an additional testosterone 5-alpha reductase inhibitor classified in Class 514, subclasses 17-, 257, 302, 312, 321, and 322.

Invention IX: Claims 8-11, 13-15, 18, 19, 21, and 22 (in-part) drawn topharmaceutical compositions and methods of use comprising a spiral compound according to one of Inventions V-VIII and an additional testosterone 5-alpha reductase inhibitor. This invention is classified in Class 514, subclasses 170, 193, 278, and 323.

Lack of Unity of Invention has been found to exist since each invention is structurally dissimilar, lacking common core structure as is evidenced by the separate classification, and thus, not so linked as to form a single inventive concept. Furthermore, the technical relationship between each invention is substantially different.